pISSN 0898-5901 | eISSN 1884-7269
Indexed in Scopus

Volume 31 - N. 1

Infectious keratitis after photorefractive keratectomy, femtosecond-LASIK and lenticule extraction in a 100,000-eye case series

Antonio Leccisotti,[1,2] Stefania V. Fields,[1] Giuseppe De Bartolo,[1] Christian Crudale[1]

[1]Siena Eye Laser, Poggibonsi, Siena, Italy; [2]School of Biomedical Sciences, Ulster University, Coleraine, UK

ABSTRACT

This study evaluates the incidence and outcome of infectious keratitis after laser vision correction by photorefractive keratectomy (PRK), femtosecond LASIK, and keratorefractive lenticule extraction (KLEx) in a retrospective, consecutive, single-institute series. Patients with presumed infectious keratitis between 2011 and 2023 were analyzed. In PRK, manual deepithelialization was done, and mitomycin C was used with spherical equivalents greater than 3 diopters. Femtosecond LASIK and KLEx were performed with an LDV Ziemer laser; the interface was rinsed in both techniques. All treatments received post-operative netilmicin eyedrops. Finally, 106269 eyes of 54278 patients were included; 6 eyes of 6 patients were identified as having infectious keratitis (3 by staphylococci, 3 culture-negative). The overall incidence of infectious keratitis was 0.0056% (0.0164% after PRK, 0.0023% after femtosecond LASIK, 0.1366% after KLEx; Chi^2 $p<0.00001$). The odds ratio for PRK compared to LASIK was 7.2 (p=0.0307); for KLEx compared to LASIK 59.7 (p=0.0008). Presentation after KLEx (2 days) was earlier than after PRK (5, 4, and 5 days) and LASIK (6 and 4 days). In all cases, hourly fortified cefazolin and tobramycin eyedrops were used, with a good response: 3 eyes maintained a 20/20 uncorrected visual acuity; 2 eyes 20/20 with myopic astigmatism; 1 eye ended 20/25 with correction because of irregular astigmatism. In conclusion, infectious keratitis was a rare complication, more common after KLEx and less common after femtosecond-LASIK. Only 3/6 cases had a positive culture. All the cases in our series had a favorable outcome.

Key words: photorefractive keratectomy (PRK), LASIK, lenticule extraction (KLEx), infection, keratitis.

Corresponding author:
Antonio Leccisotti, Largo Usilia 31, 53036 Poggibonsi (SI), Italy.
Tel.: +39 335 8118324.
E-mail: leccisotti@libero.it

Received: 29 January 2024.
Accepted: 14 February 2024.

Laser Therapy

Laser Therapy 2024; 31:389
doi:10.4081/ltj.2024.389

Introduction

Modern laser vision correction is performed by 3 leading techniques: i) photorefractive keratectomy (PRK) and other variants of surface ablation, ii) laser in situ keratomileusis (LASIK), in which a flap is created by a femtosecond laser or a mechanical microkeratome, and iii) femtosecond laser keratorefractive lenticule extraction (KLEx).[1] Given the different surgical procedures and post-operative courses, different risks of infection could be expected. In recent times, infection after PRK and LASIK has been reassessed by a large multicenter study, revealing a low risk for both procedures (0.013% after PRK and 0.0046% after LASIK).[2] A meta-analysis has however questioned these data, indicating a higher risk for LASIK, compared to surface ablation; risk factors included epithelial defects, use of contact lenses, and post-operative steroid drops; the most common causative microorganisms were fungi, streptococci, and staphylococci.[3] On the other hand, KLEx is a relatively new technique,[4] and infectious keratitis has only been the subject of a few reports, indicating a markedly higher incidence (0.28%),[5] but not comparing it with the other techniques.

We have therefore conducted a retrospective study, to evaluate the incidence and outcome of infectious keratitis after PRK, femtosecond LASIK, and KLEx in a large, single-institute series, in which anti-infectious prophylaxis and treatment were uniformly administered.

Materials and Methods

A retrospective, non-comparative study was designed, including consecutive patients undergone laser vision correction for myopia, hyperopia, and astigmatism, in a single-institute series, from November 2011 to April 2023. The Institutional Review Board provided approval on June 13, 2021. The research followed the tenets of the Declaration of Helsinki.

To identify the cases, the study used the same criteria validated by a recent article. Our refractive surgery center keeps a record of all proven or suspected infective complications that occurred within the first post-operative 12 months. The diagnosis was based on slit-lamp examination (corneal infiltrates compatible with infection, hyperemia), subjective symptoms (pain, blurred vision), and culture. Such records were reevaluated by the authors and classified as culture-proven infectious keratitis, probable culture-negative infectious keratitis, and non-infectious keratitis. In our institute, the indications for the different procedures have changed over the years: the use of surface ablation has considerably diminished, progressively replaced by femtosecond LASIK and KLEx. Nevertheless, the pre-, intra-, and post-operative measures to prevent infection have remained constant throughout the whole study period.

Soft contact lens use was interrupted 1 month before examination and surgery; rigid contact lens use was interrupted 3 months before examination and surgery. All patients were informed about the surgical procedure and provided written consent.

No preoperative antibiotics were used. All procedures were performed under topical anesthesia (2 drops of oxybuprocaine), with both eyes in the same session when a bilateral treatment was planned. To compensate for cyclotorsion in the supine position, in eyes with astigmatism >1.25 diopters (D) the horizontal axis was marked at limbus at 3 and 9 o'clock with a Codman surgical marking pen (Johnson & Johnson) at the slit-lamp. The surgeon wore a gown, surgical mask, and surgical gloves, which were changed for every patient. Each eye was treated with a new, sterile instrument set.

Post-operative visits, including slit-lamp examination, were done at 1 day, 5 days, 1, 3, and 12 months for all procedures.

PRK

A solid blade eyelid speculum (Malosa MMSU1488S) was used. Manual deepithelialisation was performed with a blunt golf club spatula. After excimer ablation, 10 mL of balanced salt solution (BSS) at 10°C was dripped onto the cornea. In eyes with myopic spherical equivalent greater than 3 D and in all hyperopic eyes, the cornea was dried by a microsponge (Merocel, Beaver Visitec), and another microsponge soaked with mitomycin-C (MMC) 0.2 mg/mL (corresponding to 0.02%) was placed on the stromal bed for 10 to 40 seconds, followed by a final irrigation with 30 ml of balanced salt solution at 10°C. Topical netilmicin 0.3% and diclophenac 0.1% were instilled, and a balafilcon A bandage contact lens (Bausch & Lomb PureVision) was applied. Topical postoperative treatment consisted of netilmicin 0.3% eyedrops 5 times daily until epithelialization; unpreserved 0.1% hyaluronic acid as a

lubricant as needed; and unpreserved diclophenac for pain relief (only for the first 3 days). When epithelialization was completed (usually 3–5 days), the bandage contact lens was removed, sodium hyaluronate eyedrops were continued, netilmicin eyedrops were stopped, and 0.1% unpreserved fluorometholone eyedrops were started 4 times daily, and tapered during the first 4 months.

Femtosecond LASIK

Our technique for femtosecond laser LASIK has been described.[6] A wire eyelid speculum was used in the phase of flap cut (Malosa MMSU1290S), to increase the space for the suction ring. A drop of unpreserved 0.2% sodium hyaluronate was dripped on the cornea. An LDV femtosecond laser Z2, Z4, or Z8 was used (Ziemer Group, Port) to create the flap; a sterile procedure pack was provided for each patient. After the completion of the laser phase, in which a flap with a superior hinge and a thickness of 90 to 120 microns was formed, the eyelid speculum was changed with a solid blade speculum (Malosa MMSU1488S), to reduce the contact with the eyelids. The flap was then separated and folded in a "taco" fashion with a flap spatula (MMSU1171, Malosa Surgical). After the refractive treatment with an excimer laser, the flap was repositioned, interface washed with BSS for 2 seconds through a single-use 25-G cannula, and the flap was finally smoothed down with a wet microsponge. A drop of unpreserved netilmicin 0.3% + dexamethasone 0.1% was dripped on the cornea. Netilmicin and dexamethasone were continued 4 times daily for a week.

KLEx

Our technique for femtosecond laser KLEx has been described.[7] A wire eyelid speculum was used in the phase of flap cut. A drop of unpreserved 0.2% sodium hyaluronate was dripped on the cornea. An LDV femtosecond Z8 with the CLEAR application was used (Ziemer Group, Port) to delineate the lenticule; a sterile procedure pack was provided for each patient. After the laser phase, the wire eyelid speculum was changed with a solid blade. The lenticule was separated with a Reinstein Separator and extracted with tying forceps (Malosa MMSU1414CS). The interface was rinsed with BSS for 2 seconds through a single-use 25-G cannula. The postoperative care was as after LASIK.
Statistical analysis was performed with the SPS software, available online at www.statisticsfordataanalysis.com (accessed 7 July 2023).

Results

Incidence

A total of 106269 eyes of 54278 patients were finally included in the study; 6 eyes of 6 patients were identified as having infectious keratitis (3 culture-proven, 3 culture-negative, probable infectious keratitis). Table 1 reports the characteristics of each treatment group, and Table 2 the features of the eyes with infection. The general incidence of infectious keratitis was 0.0056%; in detail, it was 0.0164% after PRK, 0.0023% after femtosecond LASIK, 0.1366% after KLEx (Chi^2 test of independence: 27.7568; p <0.00001). Using the LASIK group as the reference group, the odds ratio (OR) for PRK compared to LASIK was 7.2 (95% confidence interval [95%CI] 1.2 to 43.0; p=0.0307); OR for KLEx compared to LASIK was 59.7 (95% CI 5.4 to 659.4; p=0.0008).
The mean age of patients having an infection was 38.5 years; the difference with the total mean age (39.6 years) was not significant at the t-test (t: 0.345, p=0.731; 95% CI -6.7 to 4.7). All eyes developing an infection were primary treatments for myopia and myopic astigmatism, with all patients undergoing bilateral treatment except for

Table 1. Incidence of infectious keratitis after laser vision correction. Asterisks indicate p<0.01 at Chi^2 test of independence.

Procedure	Eyes (patients)	Mean age	Cases of infection	Incidence (1:x)	Odds ratio	
Photorefractive keratectomy	18222 (9339)	37.3	3	0.0164%*	4,259722222	7.2 (p=0.0307)
Femtosecond LASIK	87315 (44530)	40.1	2	0.0023%*	1:43658	Reference group
Lenticule extraction	732 (409)	38.5	1	0.1366%*	1:732	59.7 (0.0008)
Total	*106269 (54278)*	*39.6*	*6*	*0.0056%*	*1:17712*	

patient 4. All 3 PRK eyes had received MMC. No eye had been marked for astigmatism. No systemic or ocular predisposing factors were evidenced, except for a history of blepharitis in patients 4 and 6. Patient 6 (post-KLEx) had the fastest presentation, with discomfort and redness on day 2 (Figure 1); the anterior segment optical coherence tomography (AS-OCT) demonstrated that the infiltrates were located at the interface level (Figure 2).

Treatment and outcome

Infections after PRK underwent culture of the corneal scraping and, in case 2, of the bandage contact lens.
Infections after LASIK and KLEx underwent interface scraping for culture and interface washing with fortified cefazolin.
In all cases, hourly fortified cefazolin and tobramycin eyedrops were started and used until healing. All cases responded well to treatment, with the infiltrates controlled and regressing to mild opacities. Three eyes maintained a 20/20 uncorrected visual acuity; 2 eyes 20/20 with myopic astigmatism; 1 eye lost best-corrected visual acuity because of irregular astigmatism (Table 2).

Figure 1. Bacterial keratitis after refractive lenticule extraction (patient 6, left eye). The surgical incision is supero-nasal. White, paracentral round infiltrates are associated with mild corneal edema.

Figure 2. Anterior segment optical coherence tomography (AS-OCT); the surgical interface is pointed by straight arrows. One of the infiltrate is shown (curved arrow), located exactly at the interface level, surrounded by circumscribed edema (indicated by an asterisk) and with an overlying epithelial defect.

Discussion

In our series, infectious keratitis after laser vision correction was a rare event, with a total incidence of 0.0056%. All 6 cases had an early presentation (2 to 6 days), 3 with a positive culture for staphylococcus, and 3 with a negative culture. Interface washing and topical fortified antibiotics were efficacious, and best corrected visual acuity was only reduced in one eye, ending with 20/25 with correction. Compared to femtosecond LASIK, infections were 7.2

Table 2. Features and outcome of infectious keratitis after laser vision correction.

#. age, gender, eye	Procedure	Day	Microorganism	Features	Final visual acuity
1. 28, male, left	PRK	5	Negative culture	Paracentral infiltrate, pain, redness*	20/20 unaided
2. 47, female, right	PRK	4	*Staphylococcus epidermidis*	Inferior abscess, pain, redness§	20/25 +1 -2.75 x 75°
3. 33, female, right	PRK	5	*Staphylococcus epidermidis*	2 paracentral infiltrates, pain, redness*	20/20 unaided
4. 48, male, left	FS-LASIK	6	*Staphylococcus aureus*	2 paracentral infiltrates, redness	20/20 with -0.5 -1 x 45°
5. 37, male, left	FS-LASIK	4	Negative culture	Large paracentral infiltrate, pain, redness	20/20 with -1.5 x 80°
6. 38, male, left	Lenticule extraction	2	Negative culture	5 paracentral infiltrates, pain, redness	20/20 unaided

*PRK, photorefractive keratectomy; FS-LASIK, femtosecond laser in situ keratomileusis; Day, post-operative day of presentation; *onset after removal of the bandage contact lens; §onset before removal of the bandage contact lens.*

times more frequent in PRK and 59.7 more frequent in KLEx, with p <0.05 in both cases.

In the literature, the issue of infection after laser vision correction has received due attention, especially for PRK and LASIK. In major studies, the incidence of infectious keratitis after surface ablation has been estimated to be 0.017,[2] 0.019%,[8] 0.02%,[9] and even 0.21%.[10] After LASIK (by microkeratome and femtosecond laser), it was 0.0046%[2] and 0.031%.[11] Higher incidences were found, both for surface ablation and LASIK, in earlier reports.[10,11]

Our data are aligned with the most recent and largest series (564165 eyes),[2] also regarding the higher incidence of surface ablation versus LASIK. The susceptibility of surface ablation to infection can be explained by the persistence of a large epithelial defect for several days and the use of a bandage contact lens, which can easily become contaminated.[12] In LASIK, the interface is washed after ablation, and a minimal epithelial defect is created at the flap edge, healing in a few hours.

Nevertheless, despite being characterized by an even smaller linear epithelial defect (2-3 mm) at the incision site, KLEx has shown a relatively high infection rate, both in a previous report (0.2778%)[5] and in our study (0.1366%). In our patient, the presentation was early (less than 48 hours), with multiple infiltrates distant from the surgical incision, compatible with intra-operative dissemination during manual lenticule dissection. Being the peri- and post-operative pharmacological treatment and the laser platform identical to LASIK, a single difference can be identified in the efficacy of interface rinsing, less accurate in KLEx due to a closed space. Also in the literature, the presentation of infectious keratitis after KLEx is often precocious (1-3 days post-operatively)[13-15] compared with LASIK (mean: 8.7 days)[2] and PRK (mean: 5.8 days).[2] Only in 2 reports did the infectious process seem to initiate from the incision site,[15,16] while in others the incision seems uninvolved.[5,14,17]

In the literature, several microorganisms have been identified as causative, the most common being staphylococci, fungi, and streptococci.[3] Nocardia, acanthameba, atypical mycobacteria, and corynebacteria were also identified.[18,19] These data correlate well with our findings, indicating staphylococci as the only cultured microorganisms.

Risk factors identified by previous studies are dry eye,[10,20] eyelid infection,[9] exposure,[10] trauma,[20] lack of asepsis or perioperative antibiotics,[20,21] healthcare working,[22] and contact lens manipulation.[22] In our series, the only predisposing factor was, in 2 cases, a history of blepharitis.

This study has some limitations. First, the retrospective design, which was however useful for detecting such a rare complication. Second, the presumed diagnosis in cases with negative culture can be questioned, although the 3 negative cases had a classical bacterial keratitis presentation. Third, statistical evaluation of some parameters (e.g. presentation time) was impossible, due to the small number of events.

The strength of this study was the uniformity of treatment and follow-up for the 3 surgical treatments.

Conclusions

In the present series, including more than 100,000 eyes, laser vision correction was rarely complicated by infectious keratitis, which was significantly more common after KLEx and less common after femtosecond-LASIK. Only 3/6 cases had a positive culture, always for staphylococci. All the cases in our series had a favorable outcome after topical antibiotic treatment.

Conflict of interest: the authors have no conflicts of interest to declare.

Contributions: AL and SVF have contributed to the conception, drafting, final approval, and agreement to be accountable for all aspects of the work. GDB has contributed to the analysis of data, revising, final approval, and agreement to be accountable for all aspects of the work. CC has contributed to the conception, analysis of data, final approval, and agreement to be accountable for all aspects of the work.

Funding: no funding received.

Ethics approval: the study has been granted an exemption from requiring ethics approval by the Institutional Review Board at Siena Eye Laser. Ethical approval is not required for this study by national guidelines.

Data availability: All data generated or analyzed during the study are included in this article.

References

1. Ang M, Gatinel D, Reinstein DZ, et al. Refractive surgery beyond 2020. Eye 2021;35:362–82.
2. Schallhorn JM, Schallhorn SC, Hettinger K, Hannan S. Infectious keratitis after laser vision correction: incidence and risk factors. J Cataract Refract Surg 2017;43:473–9.
3. Afsharpaiman S, Zare M, Yasemi M, et al. The prevalence of infectious keratitis after keratorefractive surgery: A systematic review and meta-analysis study. J Ophthalmology, 2020;2020:6329321.
4. Sekundo W, Kunert KS, Blum M. Small incision corneal refractive surgery using the small incision lenticule extraction (SMILE) procedure for the correction of myopia and myopic astigmatism: results of a 6 month prospective study. Br J Ophthalmol 2011;95:335–9.
5. Ivarsen A, Asp S, Hjortdal J. Safety and complications of more than 1500 small-incision lenticule extraction procedures. Ophthalmology 2014;121:822-8.
6. Leccisotti A, Fields SV, De Bartolo G. Femtosecond-LASIK retreatments after primary myopic photorefractive keratectomy. Cornea 2023;42:675-9.
7. Leccisotti A, Fields SV, De Bartolo G. Refractive corneal lenticule extraction with the CLEAR femtosecond laser application. Cornea 2023;42:1247-56.
8. Wroblewski KJ, Pasternak JF, Bower KS, et al. Infectious keratitis after photorefractive keratectomy in the United States Army and Navy. Ophthalmology 2006;113:520–5.
9. Leccisotti A, Bartolomei A, Greco G, Manetti C. Incidence of bacterial keratitis after photorefractive keratectomy. J Refract Surg 2005;21:96.
10. de Rojas V, Llovet F, Martínez M, et al. Infectious keratitis in 18651 laser surface ablation procedures. J Cataract Refract Surg 2011;37: 1822–31.
11. Llovet F, de Rojas V, Interlandi E, et al. Infectious keratitis in 204,586 LASIK procedures. Ophthalmology 2010;117:232–8.
12. Hondur A, Bilgihan K, Cirak MY, et al. Microbiologic study of soft contact lenses after laser subepithelial keratectomy for myopia. Eye Contact Lens 2008;34:24–7.
13. Li J, Ren SW, Dai LJ, et al. Bacterial keratitis following small incision lenticule extraction. Infect Drug Resist 2022;15:4585–93.
14. Ganesh S, Brar S, Nagesh BN. Management of infectious keratitis following uneventful small-incision lenticule extraction using a multimodal approach – A case report. Indian J Ophthalmol 2020;68:3064-6.
15. Chehaibou I, Sandali O, Ameline B, et al. Bilateral infectious keratitis after small-incision lenticule extraction. J Cataract Refract Surg 2016;42:626-30.
16. Liu HY, Chu HS, Chen WL, et al. Bilateral non-tuberculous mycobacterial keratitis after small incision lenticule extraction. J Refract Surg 2018;34:633-6.
17. Chan TC, Chow VW, Jhanji V. Collagen cross-linking with photoactivated riboflavin (PACK-CXL) for bacterial keratitis after small incision lenticule extraction (SMILE). J Refract Surg 2017;33:278-80.
18. Garg P, Chaurasia S, Vaddavalli PK, et al. Microbial keratitis after LASIK. J Refractive Surg 2010;26:209–16.
19. Patel NR, Reidy JJ, Gonzalez-Fernandez F. Nocardia keratitis after laser in situ keratomileusis: clinicopathologic correlation, J Cataract Refractive Surg 2005;31:2012–5.
20. Karp CL, Tuli SS, Yoo SH, et al. Infectious keratitis after LASIK. Ophthalmology 2003;110:503–10.
21. Chang MA, Jain S, Azar DT. Infections following laser in situ keratomileusis: an integration of the published literature. Surv Ophthalmol 2004;49:269–80.
22. Donnenfeld ED, O'Brien TP, Solomon R, et al. Infectious keratitis after photorefractive keratectomy. Ophthalmology 2003;110:743–7.