Outcomes of Laser In Situ Keratomileusis and Photorefractive Keratectomy in Patients Taking Isotretinoin

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• PURPOSE: **To determine the functional outcomes of laser in situ keratomileusis (LASIK) and photorefractive keratectomy (PRK) in patients taking isotretinoin, which is contraindicated for these procedures.**

• DESIGN: **Multicenter, retrospective, interventional case series.**

• METHODS: **All patients taking isotretinoin who underwent LASIK or PRK from January 2003 to September 2017 were included (Group 1). Patients were compared with those undergoing LASIK or PRK who had taken isotretinoin previously but not in the previous 6 months (Group 2). Patients were included consecutively.**

• RESULTS: **A total of 113 patients (219 eyes) were included. No significant intraoperative or postoperative complications were found. There were no significant differences between the groups in terms of visual acuity, postoperative spherical equivalent, efficacy index, predictability, or safety index. When only PRK patients were taken into account, the efficacy index ($P = .017$), postoperative sphere ($P = .041$), and postoperative astigmatism ($P < .001$) were better in Group 2, although the difference was not clinically relevant.**

• CONCLUSIONS: **In our experience, LASIK and PRK can be performed effectively and safely in selected patients taking isotretinoin. The absolute exclusion of certain systemic medications should be reconsidered. (Am J Ophthalmol 2018;192:98–103. © 2018 Elsevier Inc. All rights reserved.)**

FOLLOWING THE RECOMMENDATIONS OF THE FIRST excimer laser manufacturers, the United States Food and Drug Administration (FDA) established a group of absolute and relative contraindications for corneal refractive surgery during the early days of photorefractive keratectomy (PRK) and laser in situ keratomileusis (LASIK). Specific systemic medications were included in the list of contraindications. Isotretinoin (13-cis retinoic acid) was one such drug. According to the FDA, isotretinoin is a contraindication for LASIK.

The American Academy of Ophthalmology currently considers the use of isotretinoin to be a relative contraindication for corneal refractive surgery.[1] Furthermore, a recent review on contraindications states that laser refractive surgery should be avoided in patients taking isotretinoin.[2] It is usually advised to stop isotretinoin more than 6 months before performing laser refractive surgery, although the appropriate wait time has not been established.[3] The literature provides no evidence for an association between poor outcome of laser refractive surgery and isotretinoin.[4] Ortega-Usobiaga and associates[5] showed that amiodarone—also contraindicated—was not associated with poor results after LASIK and PRK.

The objective of the present study was to determine the outcomes of a group of patients treated with isotretinoin who underwent LASIK or PRK and whether it is beneficial to wait at least 6 months between stopping isotretinoin and undergoing laser refractive surgery.

METHODS

THIS RETROSPECTIVE CASE SERIES REVIEW COMPRISED PAtients who had undergone LASIK or PRK at Clínica Baviera, Spain, between January 2003 and September 2017. More than 40 000 refractive procedures are performed each year at the clinic, a private ophthalmologic institution with 19 centers and 84 surgeons located throughout Spain. Data collection fulfilled Spanish legal requirements, and institutional review board approval was obtained. Given the retrospective nature of the research design, no informed consent was required.

Patients who were receiving isotretinoin before surgery were identified through an electronic search of medical histories using the key words *LASIK/PRK* and *isotretinoin*. Clinical data files at the institution are computerized and contain a field labeled "indication," which includes the type of surgery each patient underwent. The 2 options available for laser corneal refractive surgery are LASIK and PRK.

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TABLE 1. Demographics of Corneal Refractive Surgery Patients Taking (Group 1) and Not Taking Isotretinoin (Group 2)

	Group 1	Group 2	*P*
Age (y): median; Q25/Q75 (range)	27; 23/31 (18-52)	27; 25/29 (18-44)	.714[a]
Sex, n (%)			.492[b]
Male	32 (39.02%)	15 (48.39%)	
Female	50 (60.98%)	16 (51.61%)	
Type of surgery, n (%)			.229[b]
LASIK	143 (20.25%)	51 (83.61%)	
PRK	15 (9.49%)	10 (16.39%)	

LASIK = laser in situ keratomileusis; PRK = photorefractive keratectomy; Q = quartile.

[a]Nonparametric Mann-Whitney test.

[b]χ^2 test.

The medical histories were reviewed to collect the following data: age, sex, eye involved, procedure type (LASIK, PRK), and postoperative corrected distance visual acuity (CDVA), postoperative uncorrected distance visual acuity (UDVA), and complications.

The patients were compared with a group of patients from the same period who had been treated with isotretinoin before undergoing LASIK or PRK. These patients had discontinued isotretinoin at least 6 months before surgery.

• **SURGICAL TECHNIQUE AND POSTOPERATIVE PROTOCOL:** Patients had stable refraction for at least 1 year before the procedure. A complete ophthalmologic examination was performed before surgery following a standard protocol to determine whether patients were suitable candidates for corneal refractive surgery. Written informed consent was obtained before surgery in each case. All procedures were performed according to standard protocols. LASIK was

TABLE 2. Preoperative Refractive Data of Corneal Refractive Surgery Patients Taking (Group 1) and Not Taking Isotretinoin (Group 2)

	Group 1 (N = 158 Eyes)		Group 2 (N = 61 Eyes)		
	Range	Distribution	Range	Distribution	*P*
Sphere (D)					
LASIK	-8.81 to +4.75	-3.25 (-4.75/-1.88)	-9.00 to +5.75	-3.50 (-4.75/-2.62)	.309[a]
PRK	-7.00 to -1.75	-2.25 (-4.00/-2.00)	-4.50 to -1.75	-3.50 (-4.00/-2.56)	0.467[a]
Total	-8.81 to +4.75	-3.25 (-4.72/-2.00)	-9.00 to +5.75	-3.50 (-4.50/-2.50)	0.275[a]
Astigmatism (D)					
LASIK	0.00 to -2.75	-0.50 (-1.00/-0.25)	0.00 to -4.50	-0.50 (-1.25/-0.25)	0.698[a]
PRK	0.00 to -1.50	-0.50 (-1.00/-0.38)	-0.50 to -1.75	-0.50 (-0.88/-0.50)	0.794[a]
Total	-0.00 to -2.75	-0.50 (-1.00/-0.25)	0.00 to -4.50	-0.50 (-1.25/-0.25)	0.561[a]
Spherical equivalent (D)					
LASIK	-9.06 to +4.88	-3.50 (-5.00/-2.19)	-9.50 to +4.25	-3.75 (-4.94/-3.00)	0.252[a]
PRK	-7.75 to -1.75	-2.75 (-4.31/-2.24)	-4.88 to -2.00	-3.94 (-4.25/-2.81)	0.374[a]
Total	-9.06 to +4.88	-3.50 (-4.96/-2.23)	-9.50 to +4.25	-3.75 (-4.75/-2.88)	0.202[a]
Mean keratometry (D)					
LASIK	39.75 to 47.50	43.50 ± 1.36	40.25 to 47.25	43.74 ± 1.51	0.289[b]
PRK	40.85 to 47.25	44.75 (41.89/45.02)	41.00 to 44.75	44.50 (43.50/44.75)	0.556[a]
Total	39.75 to 47.50	43.53 ± 1.44	40.25 to 47.25	43.74 ± 1.48	0.334[b]
UDVA (logMAR)					
LASIK	0.00 to 2.00	1.52 (0.70/1.70)	0.05 to 1.70	1.70 (1.00/1.70)	0.021[a]
PRK	0.40 to 2.00	1.00 (0.70/1.30)	1.00 to 1.70	1.70 (1.00/1.70)	0.147[a]
Total	0.00 to 2.00	1.52 (0.70/1.70)	0.05 to 1.70	1.70 (1.00/1.70)	0.006[a]
CDVA (logMAR)					
LASIK	-0.10 to 0.12	0.00 (0.00/0.02)	-0.08 to 0.09	0.00 (0.00/0.01)	0.654[a]
PRK	0.00 to 0.12	0.00 (0.00/0.01)	0.00 to 0.05	0.02 (0.01/0.02)	0.057[a]
Total	-0.10 to 0.12	0.00 (0.00/0.02)	-0.08 to 0.09	0.00 (0.00/0.02)	0.340[a]

CDVA = corrected distance visual acuity; D = diopter; LASIK = laser in situ keratomileusis; PRK = photorefractive keratectomy; UDVA = uncorrected distance visual acuity.

[a]Nonparametric Mann-Whitney test; medians and quartiles are shown under distribution.

[b]*t* test for independent samples; means ± standard deviations are shown under distribution.

TABLE 3. Postoperative Refractive Data of Corneal Refractive Surgery Patients Taking (Group 1) and Not Taking Isotretinoin (Group 2)

	Group 1 (N = 158 Eyes)		Group 2 (N = 61 Eyes)		
	Range	Distribution	Range	Distribution	P^a
Sphere (D)					
LASIK	-1.00 to +1.25	0.00 (0.00/+0.25)	-1.00 to +0.50	0.00 (0.00/+0.25)	.659
PRK	0.00 to +0.25	0.25 (0.00/+0.25)	-0.25 to +0.25	0.00 (0.00/0.00)	.041
Total	-1.00 to +1.25	0.00 (0.00/+0.25)	-1.00 to +0.50	0.00 (0.00/+0.25)	.342
Astigmatism (D)					
LASIK	-1.25 to 0.00	0.00 (-0.38/0.00)	-1.25 to 0.00	0.00 (-0.25/0.00)	.470
PRK	-0.50 to 0.00	-0.50 (-0.50/-0.25)	-0.25 to 0.00	0.00 (0.00/0.00)	<.001
Total	-1.25 to 0.00	0.00 (-0.50/0.00)	-1.25 to 0.00	0.00 (-0.25/0.00)	.651
Spherical equivalent (D)					
LASIK	-1.25 to +0.75	0.00 (0.00/0.00)	-1.25 to +0.38	0.00 (-0.12/0.00)	.138
PRK	-0.25 to +0.13	0.00 (-0.06/0.00)	-0.25 to +0.25	0.00 (0.00/0.00)	.550
Total	-1.25 to +0.75	0.00 (0.00/0.00)	-1.25 to +0.38	0.00 (-0.12/0.00)	.231
Mean keratometry (D)					
LASIK	35.50 to 47.25	40.75 (39.25/42.25)	37.00 to 47.75	40.50 (39.50/41.75)	.985
PRK	37.75 to 43.75	40.00 (39.50/42.62)	38.75 to 41.75	41.00 (40.75/41.19)	.956
Total	35.50 to 47.25	40.75 (39.25/42.25)	37.00 to 47.75	40.75 (39.62/41.75)	.950
UDVA (logMAR)					
LASIK	-0.08 to 0.15	0.00 (0.00/0.02)	-0.10 to 0.15	0.00 (0.00/0.01)	.933
PRK	0.00 to 0.13	0.00 (0.00/0.02)	0.00 to 0.02	0.00 (0.00/0.00)	.331
Total	-0.08 to 0.15	0.00 (0.00/0.02)	-0.10 to 0.15	0.00 (0.00/0.01)	.704
CDVA (logMAR)					
LASIK	-0.08 to 0.07	0.00 (0.00/0.01)	-0.10 to 0.09	0.00 (0.00/0.00)	.499
PRK	0.00 to 0.11	0.00 (0.00/0.01)	0.00 to 0.02	0.00 (0.00/0.00)	.815
Total	-0.08 to 0.11	0.00 (0.00/0.01)	-0.10 to 0.09	0.00 (0.00/0.00)	.541

CDVA = corrected distance visual acuity; D = diopter; LASIK = laser in situ keratomileusis; PRK = photorefractive keratectomy; UDVA = uncorrected distance visual acuity.

[a]Nonparametric Mann-Whitney test; medians and quartiles are shown under distribution.

performed using the Moria LSK-1 microkeratome (Microtech, Inc/Moria, Antony, France). Debridement of the epithelium in surface ablation was performed mechanically using a hockey knife with(out) 20% alcohol for 20 seconds, depending on the surgeon's preference. Mitomycin C was administered for 12-15 seconds immediately after surface ablation. Laser ablation was performed using the Technolas 217C or Technolas 217-Z-100 excimer laser (Bausch & Lomb, Munich, Germany), the Mel 80 excimer laser (Carl Zeiss Meditec AG, Jena, Germany), or the WaveLight Allegretto excimer laser (Alcon Surgical, Inc, Fort Worth, Texas, USA).

Patients were examined 12 hours, 7 days, and 1 and 3 months after surgery, unless complications required more frequent visits.

• **FUNCTIONAL AND REFRACTIVE RESULTS:** We analyzed the following parameters:

- The efficacy index, calculated as postoperative UDVA/preoperative CDVA. We excluded eyes targeted for monovision.
- The safety index, calculated as postoperative CDVA/preoperative CDVA.
- Predictability, that is, the percentage of eyes within ±1.00 diopter (D) (spherical equivalent [SE]) of the targeted correction after the procedure.

These parameters were recorded using the last refraction available after treatment and the refraction recorded at the most recent examination.

• **ANATOMIC RESULTS:** We searched for intraoperative complications (epithelial defect or flap repositioning alterations) and postoperative complications, such as dry eye (symptoms -discomfort and visual symptoms- and signs -corneal staining and filaments-) and others (recurrent epithelial erosions, interface alterations [diffuse lamellar keratitis, epithelial ingrowth], microstriae, and/or other ocular surface problems).

• **STATISTICAL ANALYSIS:** Data were analyzed at eye level, including both eyes. When analyzing differences in

TABLE 4. Visual Results of Corneal Refractive Surgery Patients Taking (Group 1) and Not Taking Isotretinoin (Group 2)

	Group 1 (N = 158 Eyes)		Group 2 N = 61 Eyes)		
	Range	Distribution	Range	Distribution	*P*
Efficacy index					
LASIK	0.70 to 1.33	1.00 (0.98/1.04)	0.70 to 1.25	1.00 (1.00/1.02)	.329[a]
PRK	0.92 to 1.05	0.99 ± 0.04	0.99 to 1.11	1.03 ± 0.04	.017[b]
Total	10.70 to 1.33	1.00 (0.98/1.03)	0.70 to 1.25	1.00 (1.00/1.03)	.107[a]
Safety index					
LASIK	0.83 to 1.33	1.00 (1.00/1.05)	0.86 to 1.25	1.01 (1.00/1.03)	.201[a]
PRK	0.92 to 1.05	1.00 ± 0.03	0.99 to 1.11	1.03 ± 0.04	.060[b]
Total	0.83 to 1.33	1.00 (1.00/1.05)	0.86 to 1.25	1.01 (1.00/1.03)	.105[a]
Predictability (%), ±1.0 D					
LASIK		99.30		98.04	.458[c]
PRK		100		100	1.000[c]
Total		99.37		98.36	.480[c]

D = diopter; LASIK = laser in situ keratomileusis; PRK = photorefractive keratectomy.
[a]Nonparametric Mann-Whitney test; medians and quartiles are shown under distribution.
[b]t test for independent samples; means ± standard deviations are shown under distribution.
[c]χ^2 test.

quantitative parameters between the groups, we first applied the Shapiro-Wilk test to determine whether the distributions were normally distributed. If the distribution was normal, we applied the *t* test; otherwise, we applied the Mann-Whitney test. The homogeneity of variances for normally distributed parameters was verified with the Levene test.

Non-normally distributed variables were expressed as median and interquartile range. Normally distributed variables were expressed as mean and standard deviation (SD). Qualitative and grouped variables were analyzed using the χ^2 test.

Because this is a retrospective study, we did not conduct power analysis in order to estimate a necessary sample size. Nevertheless, the sample sizes comprised enough eyes to make clinically relevant conclusions.

RESULTS

GROUP 1 INCLUDED 82 PATIENTS (158 EYES) WHO WERE receiving isotretinoin at the time of LASIK or PRK. The median age of the 32 men and 50 women was 27 years (range 18-52 years). The median follow-up time was 217 days (range 39-4650 days). Group 2 included 31 patients (61 eyes) who had stopped isotretinoin at least 6 months before LASIK or PRK. The median age of the 15 men and 16 women was 27 years (range 18-44 years). The median follow-up time was 213 days (range 149-352 days). The demographic and preoperative refractive data are listed in Tables 1 and 2, respectively.

Postoperative refractive data are listed in Table 3. The efficacy index, safety index, and predictability are shown in Table 4. There were no significant differences between Group 1 and Group 2 for the efficacy index. However, the efficacy index was slightly better in the PRK patients of Group 2 ($P = .017$). No significant differences were found between the groups for the safety index or for predictability.

The relationship between preoperative CDVA and postoperative UDVA (efficacy) is shown in Figure 1. The change in CDVA (safety) is shown in Figure 2. The association between the attempted SE and the SE achieved can be seen in Figures 3 (Group 1) and 4 (Group 2). The predictability within ±1.00 D was 99.37% in Group 1 and 98.36% in Group 2 (*P*: NS). All eyes had postoperative astigmatism ≤ 1.25 D (*P*: NS).

We found that postoperative sphere and astigmatism were lower in PRK patients in Group 2 than in those in Group 1 ($P = .041$ and $P < .001$, respectively). This difference was not clinically relevant. No significant differences were recorded for LASIK.

We detected no intraoperative complications (eg, incomplete flap or epithelial defect for LASIK) or postoperative complications (diffuse lamellar keratitis, epithelial ingrowth, delayed epithelial healing, clinically significant haze, and infection) in either group. No clinically significant dry eye case was found.

DISCUSSION

ISOTRETINOIN IS MAINLY USED TO TREAT SEVERE ACNE that is refractory to standard treatment. The drug alters meibomian gland epithelial cell gene expression, reduces the activity of cell survival mediators, inhibits

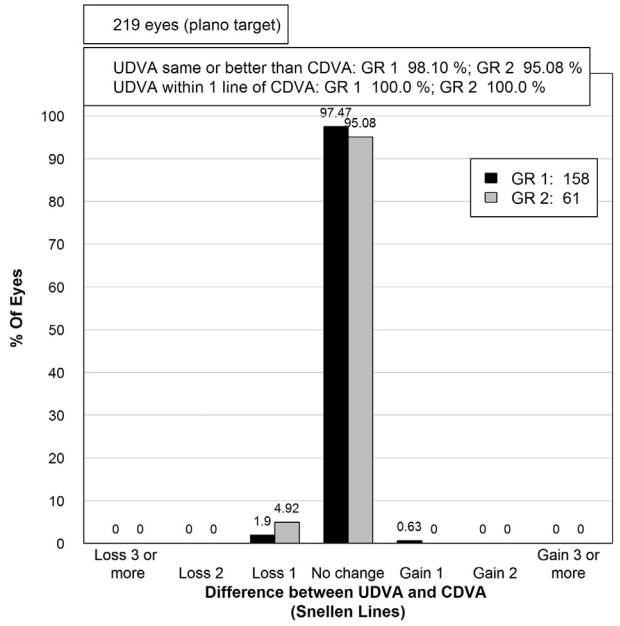

FIGURE 1. Change in visual acuity: preoperative uncorrected distance visual acuity (UDVA) vs postoperative corrected distance visual acuity (CDVA).

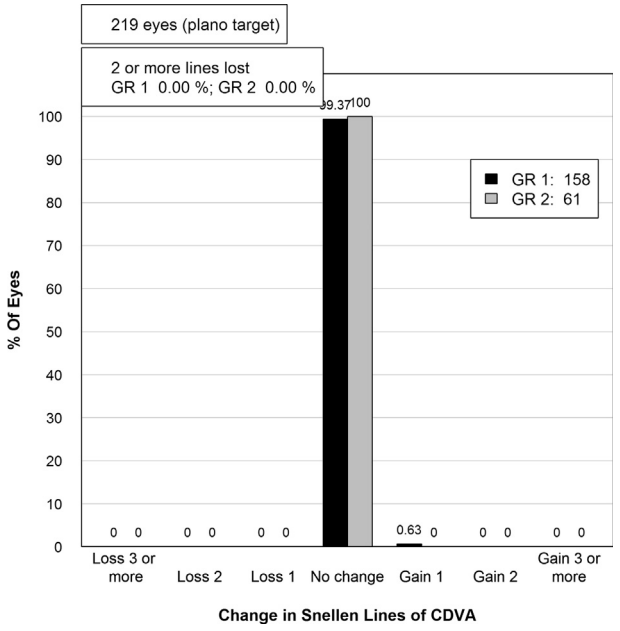

FIGURE 2. Change in corrected distance visual acuity (CDVA).

proliferation, and induces meibocyte death,[6] thus leading to dry eye, blepharitis, and conjunctivitis in over 10% of patients. Therefore, patients taking isotretinoin were included in the list of contraindications of PRK and LASIK.[7]

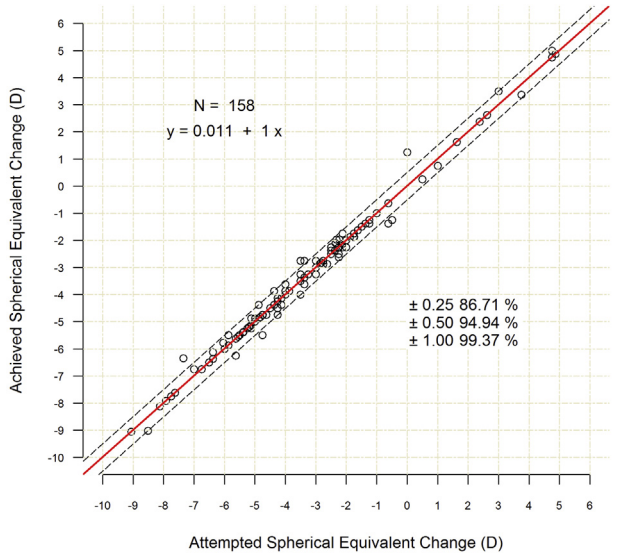

FIGURE 3. Spherical equivalent attempted vs achieved (Group 1).

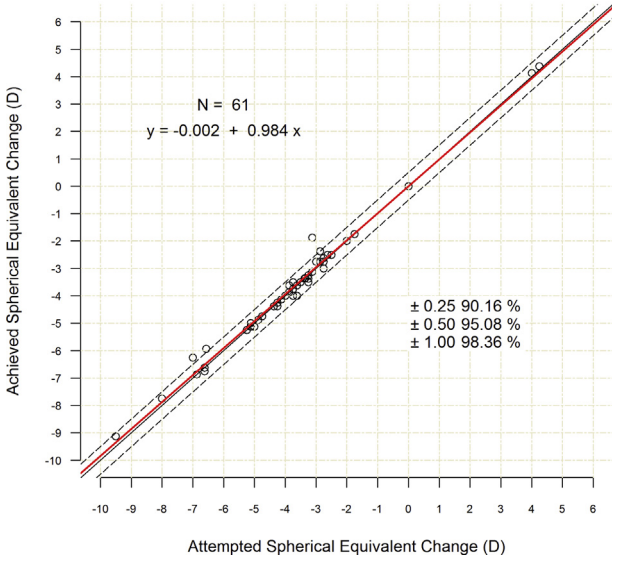

FIGURE 4. Spherical equivalent attempted vs achieved (Group 2).

The recommendation to ophthalmologists not to perform LASIK or PRK before 6 months after discontinuation of isotretinoin also means that patients who have undergone laser refractive surgery should inform their dermatologist in order not to start treatment with isotretinoin in the early postoperative period.[3]

We report the results of LASIK and PRK in patients taking isotretinoin. Although this is a retrospective study involving many centers and surgeons, data collection and classification were consistent, because each surgeon used

the same protocol, the same questionnaire, and the same software to record the clinical history. Consequently, there were no missing data in the calculation of the visual results and predictability indicators. We found that outcome was generally good after surgery, with no remarkable complications. However, the lack of complications suggests, but does not "prove," that this is safe. To our knowledge, this is the first case series of patients undergoing LASIK and surface ablation while taking isotretinoin.

Oral isotretinoin is also contraindicated for dermatologic surgery, mainly owing to the possibility of hypertrophic scars and keloid formation. The general recommendation is to wait 6-12 months after stopping medication before undergoing a dermatologic intervention.[8] However, several recent publications have questioned this contraindication, showing these procedures to be safe despite isotretinoin intake.[9]

This is a retrospective study; therefore, some additional data could have been interesting, such as Ocular Surface Disease Index questionnaire or Oxford grading at the slit lamp. Further investigation may include these issues.

Our results suggest that patients taking isotretinoin should not be excluded from corneal refractive surgery if no other contraindication is present. As with every candidate for laser refractive surgery, patients must have an unaltered tear film.

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