

The short-term effect of excimer lasers for PRK and LASIK on corneal endothelial cell density loss.

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Purpose: To study the effects of excimer lasers for PRK and LASIK procedures on corneal endothelial cell density loss compared to a control group at 30 days post-operatively.

Methods: A prospective cohort comparative study, comprised of 240 eyes from 120 patients. An excimer laser treated group who underwent PRK or LASIK procedures by Alcon Wavelight EX500 (mean age 27.83 ±8.63 years) was compared to a control group without ocular comorbidities who never had ocular procedures (mean age 32.67 ±7.88 years). Both groups were followed-up for corneal endothelial cell density (ECD) using non-contact specular microscopy on day 0 and 30 of the study period. All patients gave written informed consent and all procedures in this study were performed by one surgeon. Analysis; dependent t-test for day 0 vs 30 ECD loss and multivariable linear regression models were used to adjust for baseline differences between the two groups.

Results: For all 120 eyes in the excimer laser treated group, ECD loss at 30 days post-procedure is significantly higher than the control group (excimer laser treated group vs control group respectively; -92.44 ± 187.49 cells/mm², -7.48 ± 233.61 cells/mm², p-value <0.001). Multivariable regression model predicts ECD loss at 30 days of -60.31 cells/mm² (95% CI: $-115.53 - 5.09$, p value 0.032) or 2.41% of baseline ECD compared to control group. Each incremental 1% increase in baseline pleomorphism of endothelial cells can significantly increase the ECD loss at 30 days post-procedure by -10.06 cells/mm² (95% CI $-14.34 - -5.78$). One standard deviation increase in pleomorphism can cause an additional 3.19% of ECD loss at 30 days.

Conclusion: ECD loss at 30 days post-excimer laser procedures is significantly higher than the control group. An elevated baseline of corneal endothelium pleomorphism can exacerbate ECD loss at 30 days post excimer laser. Caution is advised regarding corneal endothelial health when selecting candidates for excimer laser treatment.

Conflicts of interest: None.

Keywords: Excimer laser, corneal endothelial cell density, LASIK, PRK, pleomorphism.

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Introduction

Excimer laser is an Argon-Fluoride laser with a wavelength of 193 nm, it is a type of laser used in corneal ablation procedures to shape the steepness of the curvature on the cornea without causing thermal damage to adjacent tissues. The uses of excimer laser in refractive surgery ranges from correction of myopia, hyperopia and astigmatism. There are two common methods in which excimer lasers are used in refractive surgery, ranging from the surface ablation method of photorefractive keratectomy (PRK) to the two-step cornea stromal flap and ablation modality laser in situ keratomileusis (LASIK). Both methods are safe and produce good outcomes.¹

The endothelial cell layer is the innermost layer of the cornea, it exhibits a hexagonal single cell layer structure, with tight junctions in between the cells which function to prevent fluid from entering the corneal stroma and pump out fluid from the cornea to maintain a relatively dehydrated and hence clear cornea. The corneal endothelial cell density (ECD) of a young adult ranges between 2,500 to 3000 cells/mm², for which the density of the cells will reduce at a rate 0.6% per year. The rate of cell density reduction can also be exacerbated by other factors such as cataract surgery.²

Carones et al.³ found that photorefractive keratectomy does not endanger endothelial cells, having performed photoablation with a central depth of 113 μ and followed up patients at 3 and 12 months postoperatively. Similarly, Juan J et al.⁴ found that LASIK does not have an effect on ECD, after having performed photoablation with a central depth of 124 \pm 19 μ and subsequent follow up at 3 and 6

months. Nevertheless, Lambert et al.⁵ studied corneas cultured in a serum-free medium post corneal ablation at a depth 150 μ and found a 60% reduction in corneal ECD when compared to corneas that have not undergone the procedure.

The effect of excimer lasers on corneal endothelial cell density is inconclusive according to current literature. Hence, our study aims to examine the effect of corneal endothelial cell density after exposure to excimer laser. We focused on postoperative outcomes of corneal endothelial cell density loss at 30 days post-procedure, comparing between patient subjects who are exposed and un-exposed to excimer lasers of both the PRK and LASIK modalities. The rationale behind the 30-day period of observation of detection of corneal ECD loss is an opinion based on our experiential observation, that it is the shortest duration of time at which corneas post-excimer laser procedures tend to become sufficiently clear for adequate examination of the endothelium using non-contact specular microscopy. While minimizing the confounding effect of the naturally-occurring rate of corneal ECD loss over time.

Methods

Subjects

This is a prospective cohort study with a population domain of patients with stable refractive error who have attended Thammasat University Hospital between 2015 and 2017. Stable refractive error is defined as having refractive power changes of less than 0.5 diopters within 1 year. Patients excluded from this study were those with concomitant non-refractive error corneal diseases, monocular patients, history of autoimmune disease, pregnancy, previous ocular

surgery, glaucoma, history of ocular trauma and retinal disease.

A total of 240 eyes from 120 patients are included in this study (Table 1). The sample size was estimated from a pilot study to have a one-tailed 0.9 power and 0.05 alpha for detecting a difference in ECD loss of >3% between two independent means. Seventy-six eyes were from 38 males and 164 were from 82 females. The cohort was divided into two groups; 1) the Excimer laser treated patients who underwent PRK or LASIK procedures (27 males and 33 females, mean age 27.83 ±8.63 years) – these patients have given informed consent and both procedures in all patients in this study were performed by a single surgeon. 2) And a control group of patients who have not undergone excimer laser-based procedures (11 males and 49 females, mean age 32.67 ±7.88 years).

Refractive surgery procedures

In our LASIK procedures, the flaps were created using a mechanical microkeratome (MK-2000; Nidek), with a flap diameter of 8.5 mm or 9.0 mm and an intended thickness of either 130 µm or 160 µm. As for our PRK procedures, the epithelium was removed by manual scraping. For both LASIK and PRK, the stroma was ablated with an Alcon Wavelight EX500 excimer laser. Emmetropia was attempted in all cases by using an optical zone diameter ranged between 6.0 to 8.0 mm.

Endothelial cell analysis

Both groups were tested for corneal endothelial cell density using non-contact specular microscopy (Nidek confoscan4 Voltage: 100/240 VAC, Freq: 50/60 Hz, Power: 300W, Fuses: 5x20mm T 5A 250V) on day 0 and 30 of the study period to determine corneal endothelial cell loss over 30

days. In the excimer laser exposed group, the date of which patients underwent their procedures is considered day 0.

Statistical analysis

Corneal ECD at 30 days post-procedure and pre-procedure baseline values for ECD, polymegatism and pleomorphism of cells, in addition to age and gender of patients were compared between the excimer treated and control group. Multivariable generalized linear models were used to adjust for any confounding factors between the two groups. We calculated the corneal ECD at 30 days post-procedure using the following equation: $\Delta ECD = ECD1 - ECD0$, in which ΔECD is change in corneal ECD 30days post-procedure, ECD1 is ECD post-procedure and ECD0 is ECD pre-procedure at day 0. A negative value for ΔECD indicates cell loss.

Ethics

This study adhered to the tenets of the Declaration of Helsinki and was approved by the Thammasat University Ethics institutional review board. Informed consent was obtained from all subjects after explanation of the nature and possible consequences of the study.

Results

For all 120 eyes in the excimer laser treated group, ECD loss at 30 days post-procedure is significantly higher than the control group. Table 1. compares the baseline patient and endothelium characteristics between the control group and the excimer laser treated group. The gender proportions and, more importantly, the mean age between the two groups differed significantly, resulting in a higher baseline polymegatism of cells.

Table 1: Baseline patient characteristics, comparing between control group and excimer laser treated group

Variable	Control Group (n = 120)			Excimer Laser Treated Group (n=120)			p-value
	Mean	SD	SE	Mean	SD	SE	
Age	32.67	±7.88	±0.74	27.83	±8.63	±0.79	<0.001
Gender	98 F† (81.67%)	22 M† (18.3%)		66 F† (55%)	54 M† (45%)		<0.001*
ECD loss at 30 days post-procedure (cells/mm ²)	-7.48	±233.61	±21.33	-92.44	±187.49	±17.11	<0.001
Baseline endothelial cell count (cells/mm ²)	2408.73	±219.81	±20.07	2503.49	±231.74	±14.87	0.997
Baseline polymegatism of endothelial cells (%)	75.07	±150.98	±13.7	58.53	±7.94	±0.72	0.125
Baseline pleomorphism of endothelial cells (%)	32.86	±5.911	±0.54	34.83	±6.91	±0.42	0.994

*Chi-square; other p-values are independent sample t-tests

†Female and Male percentages instead of mean and standard deviation

SD = standard deviation, SE = standard error

We explored the relationship between the use of excimer laser for PRK and LASIK refractive surgery and its effect on ECD at 30 days post-procedure using a univariable generalized linear model. We predicted the excimer laser treated group will result in a greater ECD loss of -89.47 cells/mm² (95%CI -138.84 – 31.10) compared to the control group (Table 2).

Table 2: Univariable analysis comparing endothelial cell count loss at 30 days postoperatively between control group and excimer laser treated group

Group	Difference in ECD loss at 30 days post-procedure (cells/mm ²)	Standard Error	95% Confidence Interval	p-value
Excimer Laser Treated Group	-84.97	±27.34	(-138.84 – 31.10)	0.002

After adjusting for the baseline differences in age, gender and endothelial cell characteristics of baseline polymegatism and pleomorphism using a multivariable generalized linear model – we predicted the ECD loss at 30 days post-procedure

would be reduced to -60.31 mm² (95%CI -115.53 – 5.09) compared to the control group (Table 3).

Table 3: Multivariable analysis comparing endothelial cell count loss at 30 days postoperatively between control group and excimer laser treated group. Adjusted for age, gender, and preoperative baseline pleomorphic endothelial cell count

Variable	Difference in ECD loss at 30 days post-procedure (cells/mm ²)	Standard Error	95% Confidence Interval	p-value
Excimer Laser Treated Group	- 60.31	±28.03	(-115.53 – 5.09)	0.032
Age	2.29	±0.17	(-0.97 – 5.56)	0.168
Male Gender	18.56	±32.59	(-45.65 – 82.77)	0.570
Baseline polymegatism of endothelial cells (%)	-0.092	±0.12	(-0.34 – 0.15)	0.458
Baseline pleomorphism of endothelial cells (%)	-10.06	±2.18	(-14.34 – -5.78)	<0.001

Discussion

In current practice, excimer lasers of both PRK and LASIK are highly effective and safe methods of surgical correction for refractive error and astigmatism. Numerous literatures suggest excimer lasers do not affect corneal ECD loss in the long term.^{3,4,6,7} However, the notion remains disputed by other literature.^{5,8} Our study focused on the short-term effects of excimer laser treatment on the corneal endothelium. Our data suggested that corneas exposed to excimer lasers for PRK or LASIK causes a significant difference in ECD loss of -60.31 cells/mm² (equivalent to 2.41% of baseline ECD loss) at 30 days post-procedure after adjusting for confounders. Our findings are in line with Pallikaris et al., who demonstrated a loss of 10.56% and 8.67% ECD loss from baseline at 12 months for PRK and LASIK respectively using Argon-Fluoride

based excimer at wavelengths of 193 nm.

Based on experience from our clinical practice, corneal haze preventing adequate examination by non-contact specular microscopy tends to resolve at 30 days. Hence our study attempted to eliminate the confounding effect of the naturally-occurring corneal ECD loss of 0.6% per year² by examining the effects of excimer lasers at the earliest feasible opportunity at 30 days post-procedure – with the goal of isolating the effect of excimer lasers on corneal ECD as thoroughly as possible. Our study had sufficient statistical power to detect a 3% difference in the rate of ECD loss between the excimer laser exposed and control groups.

Regarding other factors affecting ECD loss after excimer laser procedures. Of note, our generalized linear model suggested that each incremental 1%

increase in baseline pleomorphism of endothelial cells can significantly increase the ECD loss at 30 days post-procedure by -10.06 cells/mm² (95% CI-14.34 –5.78). A one standard-deviation increase in baseline pleomorphism (7.94% in our study) can result in an increase in corneal ECD loss of up to -79.88 cell/mm², compounding a significant additional 3.19% corneal ECD loss at 30 days post excimer laser procedure.¹⁰ On the other hand, age and gender were not found to be significant, similar to findings by Ewete et al.¹¹

Limitations

The major limitation to our study is the difference in demographics between the two recruited sample groups, resulting in the need for a multivariable analysis model to adjust for confounders. Nevertheless our prediction model suggested that age and gender was likely to be an insignificant confounder in our study. Furthermore, our study did not explore the short-term effect of stromal ablated depth and thickness of stromal residual bed on ECD loss, which the long-term effects have been previously studied.¹²

Conclusion

Excimer lasers for both PRK and LASIK procedures causes a significant reduction in corneal ECD loss at 30 days of up to 60.31 cells/mm² or 2.41% of baseline ECD, after adjustment for confounding factors and negating the rate of naturally occurring ECD loss. The short term of effect of excimer laser refractive surgery on the corneal endothelium has been clearly demonstrated. An elevated baseline of corneal endothelium pleomorphism by one standard deviation can further exacerbate ECD loss at 30 days post excimer laser procedure by an

additional 3.19%. Reflecting the effect of unhealthy corneal endothelium and its adverse reaction to excimer laser exposure. Caution should be exercised regarding corneal endothelial health when selecting candidates for excimer laser treatment.

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