

Evaluation of the Effect of Myopic Femtosecond Laser Assisted-LASIK on Anterior Chamber Flare Values and Corneal Endothelial Cells: A Prospective Before-and-After Study

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Abstract

Purpose This study aimed to investigate whether femtosecond laser-assisted LASIK (FS-LASIK) surgery causes inflammation in the anterior chamber and to analyze its effect on endothelial cells.

Methods This prospective, longitudinal study included 60 eyes of 30 patients (19 females) who had undergone FS-LASIK surgery due to myopia and myopic astigmatism. Endothelial cell density (ECD) and morphological measurements were performed using a specular microscopy, and laser flare photometry was used to measure the anterior chamber flare values on the day of surgery. iFS™ Advanced FS and VISX STAR S4-IR Wavelscan Excimer Laser platforms were used. Flare measurements were repeated on the postoperative 1st day and 7th day and the 1st and 3rd months. The endothelial measurements were repeated in the 3rd month.

Results Preoperatively, the mean flare was 5.34 ± 1.13 photons/ms; it was 6.02 ± 2.0 on the postoperative 1st day, 5.78 ± 1.98 on the 7th day, 5.77 ± 3.16 in the 1st month, and 5.45 ± 1.13 in the 3rd month. A significant difference was observed between the preoperative values and the postoperative 1st day values ($p = 0.010$). The decrease in the ECD was statistically significant, with an average of 120.3 ± 260 cell-count/mm² ($p = 0.001$) and a minimal change in the coefficient of variation ($p = 0.043$). A significant correlation was found between the increase in the flare value on the postoperative 1st day and the preoperative flare value ($r = -0.281$, $p = 0.015$). A significant correlation was found between the decrease in ECD and the preoperative ECD ($r = 0.434$, $p < 0.001$)

Conclusion FS-LASIK only causes minimal inflammation in the anterior chamber on the 1st preoperative day; additionally, a statistically significant decrease of 4.2% and minimal morphological changes were noted in the endothelial cells.

Introduction

The femtosecond (FS) laser is a type of neodymium laser with a near-infrared ray wavelength (1053 nm). It can focus with very short pulses of $1/10^{15}$ of a second and make incisions by creating cavitation bubbles and a split interface during photo-destruction of the corneal stroma [1, 2].

The use of FS in ophthalmology began in the early part of the 21st century and marked a new era in corneal refractive surgery. It has been shown to create laser in-situ keratomileusis (LASIK) flaps as well as or even better than mechanical microkeratomes (MMKs) [2–4]. FS-assisted LASIK (FS-LASIK) promises more predictable flaps and fewer flap complications, less ocular aberrations, better uncorrected visual acuity (UCVA), less variation in intraocular pressure, and less dry eye. However, complications, such as rainbow-like glare, haze, diffuse lamellar keratitis, and opaque bubble, cannot be ignored [2, 5–8].

The inflammation expected in corneal refractive surgery occurs in the corneal stroma; moreover, the inflammation that causes complications is often at the stromal interface [9–11]. However, it has been previously shown that refractive surgical procedures can have mechanical, photo-destructive, and

photochemical effects on the cornea, and may stimulate apoptosis; inflammatory pathways and arachidonic acid metabolites can also cause inflammation in the anterior chamber [11–15].

Several studies have investigated the effect of FS laser-assisted cataract surgery on anterior chamber inflammation and corneal endothelium [16–18]. Furthermore, the effects of LASIK performed with MMKs, excimer laser with superficial ablation as photorefractive keratectomy (PRK), and even radial keratotomy and intrastromal rings on inflammation in the anterior chamber have been investigated [12, 19, 20]. Since FS-LASIK surgery is applied using both an FS laser and an excimer laser, we aimed to determine the direct and indirect effects of these applications on the corneal endothelium, the intensity of the inflammation, and the blood-aqueous barrier in the anterior chamber. To the best of our knowledge, the effects of FS-LASIK on anterior chamber inflammation have not been previously investigated. Therefore, we evaluated these effects using objective measurement methods, such as specular microscopy and laser flare photometry.

Materials And Methods

Sixty eyes of 30 patients who underwent FS-LASIK surgery at the Department of Ophthalmology, Istanbul University Istanbul Faculty of Medicine between December 2019 and March 2020 were included in this prospective clinical study. Approval for the study was obtained from the institute's Ethics Committee (06.12.2019/20/1495), and signed informed consent was obtained from all the patients. The study was conducted in accordance with the ethical values stipulated in the Helsinki Declaration.

Inclusion criteria

Patients older than 18 years of age, with a stable refraction in the previous year, eligible for LASIK surgery based on ophthalmological and topographic tests, or undergoing uncomplicated FS-LASIK surgery only because of myopia or myopic astigmatism were included.

Exclusion criteria

Patients who did not show up for the postoperative follow-up were excluded. Patients with hyperopia, hyperopic or mixed astigmatism, eyes found to be unsuitable for LASIK surgery, such as those with corneal ectasia, fruste keratoconus, and significant anterior or posterior elevation based on ophthalmological and topographic tests, and patients who underwent superficial ablation or other refractive surgery modalities or complicated LASIK were also excluded.

A complete ophthalmological examination was performed on the patients at each visit. Uncorrected distal visual acuity (UDVA) and corrected distal visual acuity (CDVA) were measured using decimal charts and were converted into logarithm of minimum angle of resolution (logMAR). Manifest and cycloplegic refractions were determined, and intraocular pressures were measured. Detailed anterior segment and fundus examinations were performed. Preoperatively (pre-op), corneal topographies were obtained using

Pentacam® HR (OCULUS Optikgeräte GmbH, Wetzlar, Germany) and evaluated carefully on a quadruple refractive map to determine suitability for refractive surgery.

On the day of surgery, endothelial cell density (ECD), coefficient of variation (CV), and hexagonality measurements were performed by specular microscopy (Cellcheck SL, Konan Medical CA, USA); the ECD was accepted as cell count/mm² within 5% of standard deviation. The anterior chamber flare values were measured by laser flare photometry (Kowa FM-700, Kowa company, Aichi, Japan); the average of three consecutive measurements was accepted as the flare value.

Surgical procedure

Refractive surgeries were performed with an iFS™ Advanced Femtosecond Laser System (150 Hz, AMO GmbH, Ettlingen, Germany) and the VISX STAR S4 IR Wavescan Excimer Laser (AMO GmbH, Ettlingen, Germany). In all the patients, the flap diameter was set as 8.8–9.0 mm, the flap thickness was set at 100–110 microns, and the ablation amounts were recorded. Postoperatively, prednisolone sodium phosphate 1%, moxifloxacin 0.5%, and artificial tear drops (trehalose + Na Hyaluronate + carbomer combination) were prescribed four-times daily. Instillation was started immediately after the procedure. The antibiotic drop was discontinued at the end of the first week, and the steroid drop was tapered after the first week and used for three more weeks. The artificial tear drops were used for three months.

Flare measurements were repeated postoperatively (post-op) on the 1st day, the 7th day, the 1st month and the 3rd month. The endothelium measurements were repeated in the 3rd month. The pre-op flare values and the flare values for post-op 1st day, 7th day, 1st month, and 3rd month were compared. The pre-op and 3rd month values of the endothelium measurements were compared.

Statistical analysis

SPSS Version 22 software program was used for statistics. A paired t-test was used in the first test-last test situations and the cross-comparisons. Pearson correlation analysis and linear regression analysis were performed to examine the relationship between the parameters and these changes. A p value less than or equal to 0.05 was considered statistically significant.

Results

A total of 60 eyes of 19 female and 11 male patients were evaluated. The mean age of the patients was 24.97 ± 3.6 years (range: 21 to 37 years). The mean central corneal thickness was 566.27 ± 32.7 microns (range: 505 to 654 microns), the mean ablation amount was 66.32 ± 27.65 microns (range: 29 to 133 microns), and the mean flap diameter was 8.92 ± 0.08 millimeters (range: 8.8 to 9.0 millimeters).

As expected, UDVA increased significantly, and the mean spherical, cylindrical, and spherical equivalent refractive errors decreased significantly in all the eyes, post-op. The mean CDVA did not change. The patient characteristics are summarized in Table 1.

Table 1
Patient characteristics

Variables/Means	Preoperative	Postoperative 3rd month	P value (t-test)
<i>UDVA (logMAR)</i>	1.18 ± 0.49	-0.02 ± 0.077	< 0.0001
<i>CDVA (logMAR)</i>	-0.023 ± 0.043	-0.040 ± 0.074	0.133
<i>Spherical R. Err (D)</i>	-3.30 ± 1.72	-0.05 ± 0.28	< 0.0001
<i>Cylindrical R. Err (D)</i>	-0.97 ± 0.89	-0.38 ± 0.29	< 0.0001
<i>Spherical Equivalent R. Err (D)</i>	-3.79 ± 1.74	-0.25 ± 0.23	< 0.0001
<i>UDVA: Uncorrected distance visual acuity; CDVA: Corrected distance visual acuity; R. Err: Refractive error; D: Diopters</i>			

The average flare value was 5.34 ± 1.13 photons/ms, preoperatively; it was 6.02 ± 2.0 photons/ms on the post-op 1st day, 5.78 ± 1.98 photons/ms on the 7th day, 5.77 ± 3.16 photons/ms in the 1st month, and 5.45 ± 1.13 photons/ms at the 3rd month. A statistically significant difference in the mean flare values was observed only between the pre-op and post-op 1st day values ($p = 0.010$). However, this difference was minimal (mean dif = 0.68 ± 1.99 photons/ms). There was no significant difference in the cross-comparison of flare values of the other post-op visits. The changes in average flare values are shown in Fig. 1 and the cross-comparisons are summarized in Table 2.

Table 2
Cross-comparison of the flare values, paired t-test (p values)

Flare Value	Preoperative	1st day	7th day	1st month	3rd month
<i>Preoperative</i>		0.010	0.109	0.286	0.433
<i>1st day</i>	0.010		0.491	0.607	0.059
<i>7th day</i>	0.109	0.491		0.997	0.238
<i>1st month</i>	0.286	0.607	0.997		0.416
<i>3rd month</i>	0.433	0.059	0.238	0.416	

Change in flare values (photons/ms) over time

The decrease in the mean ECD was statistically significant, with an average of 120.3 ± 2.60 (4.2%) cell count/mm² ($p = 0.001$). While evaluation of the endothelial cell morphology showed that the increase in

the CV for cell size was slightly statistically significant ($p = 0.043$), hexagonality did not change significantly ($p = 0.058$). The changes in corneal endothelial cells are summarized in Table 3.

Table 3
Endothelial cell assessment: ECD and morphological features

Variables	Preoperative	Postoperative 3rd months	p value (paired t-test)
<i>Endothelial cell density (ECD) (cell/mm²)</i>	2867.1 ± 230.7	2746 ± 262.2	0.001
<i>Coefficient of Variation (CV) in cell size</i>	27.2 ± 2.7 (23–35)	27.6 ± 2.8 (22–37)	0.043
<i>Hexagonality (%)</i>	58.8 ± 3.7 (51–67)	58.4 ± 3.5 (50–65)	0.058

The relationships between the parameters and the increase in the flare value on post-op 1st day and the decrease in ECD were investigated using multiple regression analysis. A significant correlation was found between the decrease in ECD and the pre-op ECD ($r = 0.434$, $p < 0.001$). A significant correlation was found between the increase in the flare value on post-op 1st day and the pre-op flare value ($r = -0.281$, $p = 0.015$). No relationship was found between both endothelial loss and flare elevation and the other parameters, such as pre-op spherical, cylindrical, spherical-equivalent refractive errors amounts, ablation dept, UCVA, CDVA, and CCT. The correlations were summarized in Table 4.

Table 4

Correlations for flare elevation on the post-op 1st day and endothelial cell loss (linear regression analysis)

Parameters	<i>Correlations between Flare Elevation & Variables</i>		<i>Correlations between Endothelial Loss & Variables</i>	
	<i>Pearson r=</i>	<i>p=</i>	<i>Pearson r=</i>	<i>p=</i>
<i>Preoperative UCVA</i>	0.109	0.205	-0.44	0.369
<i>Preoperative CDVA</i>	-0.048	0.357	0.030	0.410
<i>Preoperative Spherical R. Err.</i>	-0.139	0.145	0.080	0.271
<i>Preoperative Cylindrical R. Err.</i>	0.121	0.179	0.143	0.137
<i>Preoperative Spherical. Equivalent</i>	-0.108	0.205	0.114	0.194
<i>Preoperative CCT</i>	0.074	0.286	-0.112	0.198
<i>Ablation Dept</i>	0.087	0.254	0.128	0.165
<i>Preoperative Flare value</i>	-0.281	0.015	-0.037	0.388
<i>Preoperative Endothelial Count</i>			0.434	< 0.001
<i>CCT: Central corneal thickness; UDVA: Uncorrected distance visual acuity; CDVA: Corrected distance visual acuity; R. Err: Refractive error</i>				

Discussion

The present study found a statistically significant but minimal increase in flare value on the post-op 1st day after FS-LASIK; however, no significant difference was found between the pre-op values and the values for the other post-op visits. We only found a negative and weak correlation between the flare elevation on the post-op 1st day and the pre-op flare value.

However, in other studies on anterior chamber inflammation related to other corneal refractive surgeries, such as LASIK performed with MMKs, El Harazi et al. [19] investigated anterior chamber inflammation after LASIK was performed with MMKs and reported high flare values only on the 1st post-op day; they did not find a correlation for this elevation. The values returned to normal on the 7th day post-op. Sen et al. [21] reported that the flare values increased in the first hours after performing the LASIK procedure to correct high astigmatism in patients treated with penetrating keratoplasty before surgery, but decreased to normal levels even on the 1st day. Pisella et al. [20] reported high and prolonged inflammation after LASIK (performed with MMKs); they reported that the increase in the amount of flare was greater on the 1st day post-op, especially in eyes undergoing LASIK; however, they also reported that the flare values

returned to normal levels on the 7th day post-op in PRK, but this period was prolonged in LASIK and no significant increase in a flare was observed at any time in patients who underwent intrastromal ring implantations. Pérez Santonja et al. [22] reported that, after LASIK with MMKs, there was no increase in the flare values on the 1st, 3rd, and 7th days, post-op. Interestingly, they also reported that the flare values decreased after the 2nd week in comparison to the pre-op value, and they only reached typical values in the 3rd month, post-op.

Our findings suggest that FS-LASIK does not cause a significant increase in inflammation in the anterior chamber, and it does not cause severe damage to the blood-aqueous barrier. The minimally elevated flare values on the 1st day and the near-normal values of consecutive post-op visits may be related to the use of topical steroid drops instilled immediately after surgery and easily controllable mild inflammation. As mentioned above, in the literature, the presence of more pronounced inflammation findings after LASIK performed with MMK in comparison to the values we found with FS-LASIK suggests that MMK is more associated with inflammation than FS-LASIK. To the best of our knowledge, no previous study has investigated anterior chamber inflammation related to FS-LASIK. Our study is the first to report on anterior chamber flare values after FS-LASIK.

We found a statistically significant mean ECD decrease of 4.2% and a modest change in cell morphology at the end of the 3rd post-op month for patients undergoing FS-LASIK. The only significant correlation was between endothelial loss and the pre-op ECD. In contrast, Tomita et al. [23] reported no significant changes in ECD and its morphologies three months after FS-LASIK surgery was performed with two different FS platforms, and no difference was found between the two platforms. In their series of 21 patients comparing FS-assisted LASIK with MMKs, Klingler et al. [24] also reported no significant change in the ECD in both techniques at the end of a 5-year follow-up. In the literature, it has been reported that there is no significant decrease in ECD after PRK [25–26]. Collins et al. [27] reported that they did not detect any change in the endothelium in the 3-year follow-up after LASIK was performed with MMKs. Durrie et al. [28] compared PRK with thin-flap LASIK and reported no significant changes in the ECD at the 3rd post-op month with both techniques and no difference between the two techniques.

The present study found a modest decrease in ECD and a minimal increase in the CV value, thus contradicting the findings reported in the literature mentioned above. However, the reduction in ECD is less than 5%, and it does not have clinical significance in healthy eyes. These findings suggest that endothelial cells may be trying to compensate for the decrease in ECD via polymegatism. Similar to our study, a recently published study by Shaaban et al. [29] reported a statistically significant decrease in ECD and a change in endothelial morphology, although clinically insignificant in both FS-LASIK and small incision lenticule extraction (SMILE). The effect on the endothelial cells may be related to the heat energy generated by the shock waves that occur when the flap is created with the FS laser. This signals that it is important to be careful in cases with endothelial abnormalities, such as endothelial dystrophy because, in the literature, there are case reports of cornea guttata or Fuchs endothelial dystrophy being decompensated after LASIK [30, 31].

This study has some limitations. It only included a small number of cases, it did not include a control or comparison group, and, due to the post-op treatment protocol and ethical reasons because of the risk of diffuse lamellar keratitis and regression, steroid drops were used in all patients. Moreover, the follow-up time was insufficient to enable a more realistic observation of the change in ECD. Furthermore, FS-LASIK is a two-step procedure, and it is difficult to predict from which step the effect originates. A comparison of FS-LASIK with LASIK performed with MMK, or with a procedure performed with only FS, such as SMILE, or a method with no flap, such as PRK, may provide some more helpful information. Nevertheless, in PRK, LASIK, and SMILE, the stromal depth at which the incision and ablation are made are different, which can change their effect. However, the lack of a significant change in the amount of flare reduces the need for a comparison group in order to detect which step is associated with flare change. In addition, since it is well-defined in the literature that LASIK performed with MMK does not significantly reduce the mean ECD, it may be considered that this decrease may be related to the FS laser rather than the excimer laser. The advantages of the present study are that it is a prospective, longitudinal study, and objective measurement methods were used.

Conclusions

According to the present study's findings, FS-LASIK does not cause severe inflammation in the anterior chamber, and it does not significantly increase the amount of flare except for minimal elevation on the 1st post-op day. In this respect, it offers a safe profile in terms of post-op intraocular inflammation. To the best of our knowledge, the study discussed in this paper is the first to evaluate anterior chamber inflammation and report flare values in this type of refractive surgery. Additionally, FS-LASIK was found to cause a statistically significant decrease of 4.2% in ECD, even though this decrease is minimal. If performing FS-LASIK on a patient group at risk for endothelial cells damage (e.g., family history or signs of corneal guttata, or history of previous intraocular surgery or ocular trauma), it may be beneficial to keep this finding in mind.

Declarations

The preliminary report of this study was presented as a free paper at the 38th Congress of The European Society of Cataract & Refractive Surgeons, held online 2-4 October 2020

Compliance with Ethical Standards

* This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine
(06.12.2019/20/1495)

* Informed consent was obtained from all individual human participants included in the study.

*Ethical approval: This article does not contain any studies with animals performed by any of the authors.

Consent for publication: All authors declare that they agree to the article be published in the Journal of BMC Ophthalmology.

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Figures

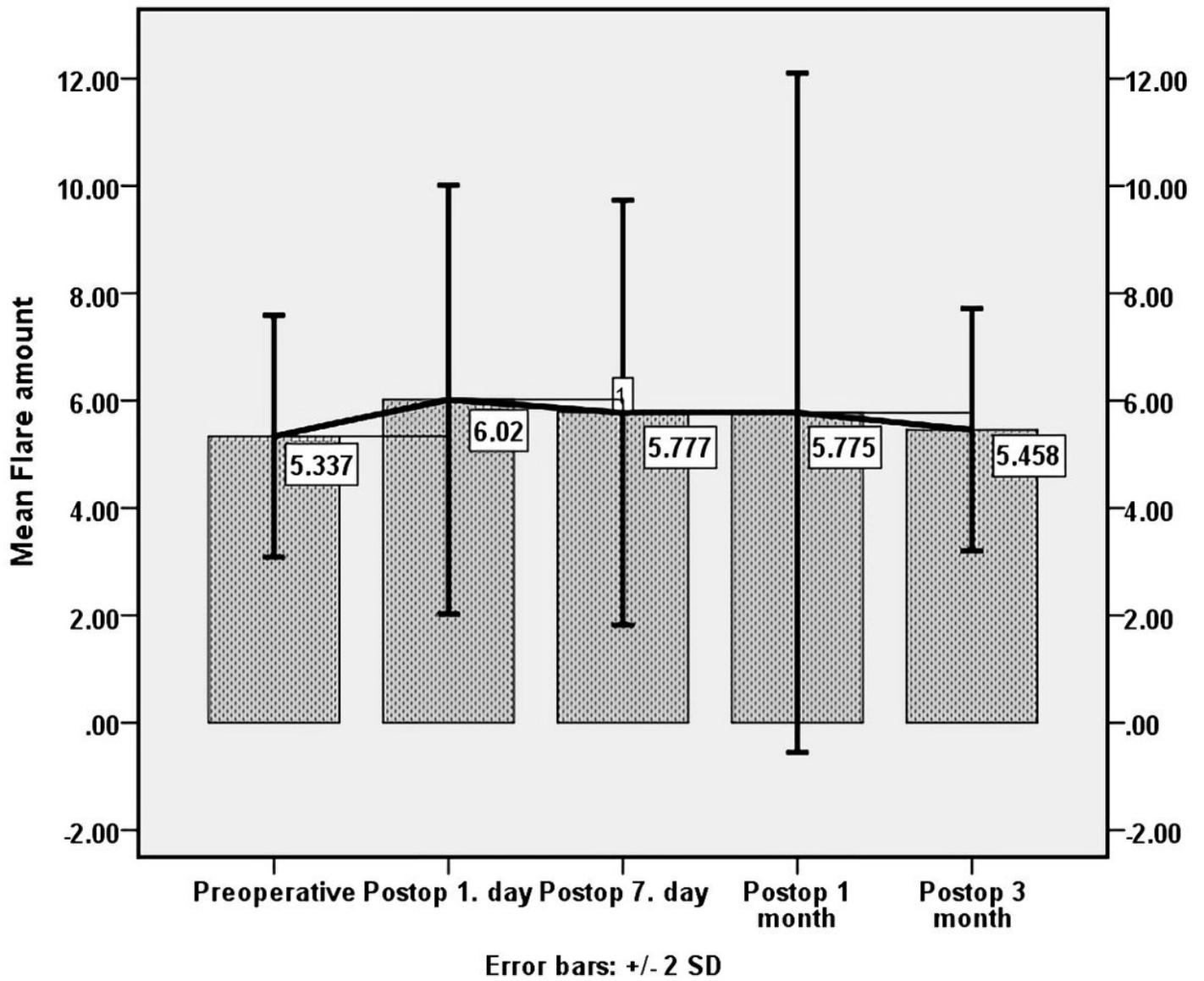


Figure 1

Change in flare values (photons/ms) over time