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Femtosecond Small Incision Lenticular Extraction in comparison to Femtosecond Laser *In situ* Keratomileusis Regarding Dry Eye Disease

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Abstract

BACKGROUND: The objective was comparison of femtosecond small incision lenticule extraction (FS-SMILE) versus Femtosecond laser *in situ* keratomileusis (FS-LASIK) regarding dry eye disease (DED) and corneal sensitivity (CS) after these refractive surgeries.

AIM: The difference between FS-SMILE and FS-LASIK regarding dry eye symptoms, signs, and corneal sensitivity post-refractive surgeries in two groups of matched patients.

METHODS: A comparative prospective study was conducted for a period of 2 years, from March 2017 to February 2019. Enrolled patients were diagnosed with myopia. Fifty patients (100 eyes) were scheduled for bilateral FS-SMILE and the other 50 patients (100 eyes) were scheduled for bilateral FS-LASIK. Both groups were followed for 6 months after surgery. The age, gender, and pre-operative refraction for both groups were matched. Complete evaluation of dry eye disease had been performed at regular intervals. The evaluation included history of symptoms according to scoring systems, investigations, and clinical examination.

RESULTS: One month postoperatively and in both groups, there was significant DED ($p < .01$), although incidence was lower in femtosecond SMILE group, overall severity score (0–4): 0.3 ± 0.3 (FS-SMILE) versus 1.4 ± 0.9 (LASIK). One month postoperatively, CS was lower in FS-LASIK more than FS-SMILE eyes (2.3 ± 2.2 vs. 3.6 ± 1.8, respectively, $p < .01$) and then shifted to non-statistically significant sensitivities at 6-month duration. DED was negatively correlated with CS ($p < 0.01$).

CONCLUSIONS: The FS-LASIK surgery had a more pronounced effect on CS and DED compared with FS-SMILE, with higher incidence of DED post-refractive surgery.

Introduction

Recently, introduced femtosecond small-incision lenticule extraction (FS-SMILE) is a procedure that gathered numerous benefits, like FS laser that is used for fashioning a corneal intrastromal lenticule that is removed manually through a small (2–7 mm length) peripheral corneal incision [1], [2]. This relatively new technique does not require a flap, which, in turn, reduces some flap related side effects of FS-LASIK, such as dislocation and related astigmatism [2], [3]. Dry eye continues to be the most frequent adverse effect after LASIK. Mild to severe ocular surface dryness symptoms are experienced by many patients, after LASIK, that are adequately controlled using artificial tears. If symptoms keep to be reported for long duration, 20–40% of patients may develop chronic dry eye disease (DED) 6 months postoperatively [4]. Proposed factors that cause DED post LASIK include corneal nerves disruption during creating the flap, in addition to damage by the excimer laser photo ablation [5]. The vast majority of factors reported to be involved in the pathogenesis of DED, such as tear secretion, quality of tear-film, healing of the epithelium of the cornea, and the rate of blinking, all could be affected post-refractive LASIK procedures [6]. The SMILE operation constitutes a minimally invasive refractive surgery for the cornea, because it merely requires a small tunnel, with less associated damage to corneal nerves, thus further protection for patients against DED [7]. Clinical studies had reported refractive results, CS, and clinical ocular surface dryness post SMILE surgeries, but nothing else has been done to estimate the overall severity of the dryness, which demands integrating objective tests along with symptoms reported subjectively by patients, as recommended by Delphi [7]. The current study aimed to investigate the difference between FS-SMILE and FS-LASIK regarding dry eye symptoms, signs, and corneal sensitivity post-refractive surgeries in two groups of matched patients.

Material and Method

Study design and setting

A comparative prospective interventional study conducted at the Refractive Surgery Center of Al Istishari Hospital, Baghdad, Iraq for a period of 20 months from March 1, 2017, to October 31, 2018.

Study population

The included patients had bilateral eyes with spherical correction range from −2 to −6 diopters and cylinder range from 0 to – 3.5 diopters and seeking for management and willing to participate in this study.

Exclusion criteria

Patients presented with sign or symptom of dry eye disease (tear film breakup time (TBUT) >10 s, Schirmer I test >10 mm/5 min), corneal or conjunctival staining, Meibomian gland dysfunction, previous ocular and or eye lid medical or surgical treatment, and pregnancy and chronic systemic disorder were excluded from the study.

Sample size

The sample size was calculated according the two proportions formula:

$$N = \frac{(Z\alpha / 2 + Z\beta)2^{*}(pSMILE(1-pSMILE) + pLASIK(1-pLASIK))}{(pSMILE - pLASIK)2} = 80.38$$

where $Z_{\alpha/2}$ equals 1.96 for confidence level of 95%, $Z\beta$ equals 1.28 for a power of 90%, and p_{SMILE} and p_{LASIK} were the expected prevalence of dry eye after 6 months in corresponding groups and were reported by Denoyer *et al*. (2015) to be 20% and 43% [8], respectively. The estimated sample size was increased to 100 eyes in each group to avoid dropouts and increase study power. Patients were assigned into two age, gender, and spherical equivalent matched equal groups:

- FS-SMILE Group: 100 eyes of 50 patients who underwent bilateral FS-SMILE.
- FS-LASIK Group: 100 eyes of 50 patients underwent bilateral FS-LASIK.

Study outcomes

All patients participated in this study attended the follow-up periods of 1 and 6 months post-refractive surgery. Outcomes were assessed using Ocular Surface Disease Index (OSDI) (0-100), Tear Break-Up Time (TBUT) (in seconds), Schirmer I test (ST-1) (in mm/5 min), Oxford score (0-5), and Dry Eye Workshop (DEWS) scale (0-4).

Ethical considerations

After the approval of Ethical Committee of Al-Istishari Hospital, informed written consent was gained from each participant, which included adequate information regarding the aim and methods of the current study.

Materials

Anterior segment spectral-domain OCT was done by (Canon, HS 100, TOKYO, JAPAN), Corneal esthesiometry, slit lamp, Fluorescein paper, and Whitnall paper.

Method/Evaluation of Dry Eye Disease

Clinical examination

All the examinations were performed 1 week preoperatively, 1 and 6 months after the surgery. The post-operative clinical examination was done by another ophthalmologist, who was masked to type of performed procedure and administered the OSDI for all patients for assessing the exact impact of DED on vision and related quality of life [9]. DEWS severity was evaluated according to an overall index (from 0 to 4) and including symptoms and signs [1], [10].

Corneal esthesiometry was performed 1 and 6 months postoperatively. The sensitivity of the cornea was measured using contact nylon thread [Cochet, Bonnet esthesiometer]. Measurements were taken and data reported as the mean of three measurements at the center of the cornea.

Investigations

1. Anterior segment OCT was done 6 months after the date of surgery. Two images of each cornea were acquired with apex measurement of corneal thickness, epithelial thickness, and the interface depth.
2. Slit-lamp examinations were conducted in a defined sequence [11] and included three TBUT measurements and their calculated mean, and the Oxford score which incorporated fluorescein staining and graded from 0 to 5.
3. ST-1 in mm per 5 min, without topical anesthesia.

Surgical technique

All surgeries were performed by single experienced surgeon under topical anesthesia [Tetracaine eye drop 0.5%] using the following technique:

- For FS-LASIK group, superior-hinge flap with 120 µm thickness, 8.0 mm diameter, and 45° side cut angles were created with 500 kHz VisuMax femtosecond laser, 160 nJ energy [Carl Zeiss, Meditec, Germany]. The spherocylindrical refractive corrections with optical zone 6.5 mm and ablation zone 8.0 mm were done by excimer laser operating system [Carl Zeiss, Meditec, MEL 90, Germany]. Automatic iris registration and pupil-tracking system were activated before photoablation.
- For FS-SMILE group, 120 µm cap thickness; 7.6 mm cap diameter; and 6.5 mm lenticule diameter were performed with 500 kHz VisuMax femtosecond laser, 160 nJ energy [Carl Zeiss, Meditec, Germany]. The patient was fixating on light target during suction procedure to a chief central lenticule. At the end, incision of 3 mm in length was created at the 130° position for lenticule extraction. In both groups, 0.3% Tobramycin and 0.1% with dexamethasone suspension (Tobradex, Alcon Laboratories) every 6 h for 2 weeks with preservative-free sodium hyaluronate were used 6 times/day for 30 days. After 1-month post-operative, sodium hyaluronate with or without lubricant gels were administered in frequency and duration according to their need.

Statistical analysis

The data were handled using the Statistical Package for Social Sciences (SPSS) version 25. Data representation included mean, standard deviation, and ranges. The frequencies and percentages presented by Categorical data. The comparison between the studded groups done continuously with variables according to independent t-test (two tailed). A level of $p < 0.05$ was considered significant.

Results

This study enrolled a total of 200 eyes that undergone refractive correction with no adverse effects reported among them. No statistically significant differences were found between the two study groups regarding age, sex, spherical equivalent myopia, and morphologic parameters as total corneal thickness (TCT), epithelial thickness, and the interface depth, as shown in Table 1.

DED 1 and 6 months postoperatively

Preoperatively, there were no statistically significant differences regarding DED between the two study groups. After 6 months, OSDI and DEWS scale were significantly lower in FS-SMILE group than that in FS-LASIK group (8.2 vs. 19.6, $p < 0.01$; and 0.3 vs. 1.4, $p < 0.01$, respectively), while TBUT was significantly higher in FS-SMILE group than that in FS-LASIK group (8.0 vs. 5.8, $p < 0.01$) (Table 2).

Table 1: Comparison between study groups by patient features, visual outcomes, and corneal morphology

Variable	FS-SMILE Group (n = 50)	FS-LASIK Group (n = 50)	p
Pre-operative			
Age (Years)	27.3 ± 5.2	28.2 ± 6.4	0.442
Gender (M/F ratio)	0.52	0.56	0.688
Spherical equivalent (D)	−4.54 ± 1.95	−4.35 ± 2.12	0.511
Six months outcomes			
Spherical equivalent (D)	−0.02 ± 0.4	0.03 ± 0.39	0.901
Distant best uncorrected visual acuity (log MAR)	0.07 ± 0.1	0.07 ± 0.1	1.0
Epithelial thickness (µm)	40.1 ± 12.2	39.9 ± 11.5	0.905
Total corneal thickness (µm)	490.6 ± 38.1	500.8 ± 39.1	0.062
Depth of the interface (µm)	118.4 ± 3.9	117.9 ± 4.8	0.419

Table 2: Dry eye disease 1 and 6 months after refractive surgery

	One month postoperatively			Six months postoperatively		
	FS-SMILE	FS-LASIK	p	FS-SMILE	FS-LASIK	p
OSDI (0–100)	20.5 ± 13.1	23.7 ± 15.2	0.08	8.2 ± 3.9	19.6 ± 5.5	<0.01
TBUT (s)	6.2 ± 1.3	5.8 ± 1.7	0.13	8.0 ± 1.6	5.8 ± 1.6	<0.01
ST-1 (mm/5′)	15.3 ± 5.6	20.2 ± 8.7	0.06	18.2 ± 9.3	17.1 ± 8.1	0.85
Oxford score (0–5)	0.06 ± 0.32	0.29 ± 0.61	0.17	0	0.38 ± 0.5	0.06
DEWS (0–4)	1.2 ± 0.7	1.7 ± 0.7	0.07	0.3 ± 0.3	1.4 ± 0.9	<0.01

The distribution of the severity of dry eye disease 1 and 6 months after SMILE versus LASIK is detailed in Table 3. One month after the surgery, there was not statistically difference between the two groups $p > 0.05$.

Table 3: Distribution of post-refractive dry eye disease 1 and 6 months postoperatively

DEWS	One month postoperatively			Six months postoperatively		
	SMILE (%) n = 100	LASIK (%) n = 100	p–	SMILE (%) n = 100	LASIK (%) n = 100	p
Zero	40 (40.0)	36 (36.0)	>.05	80 (80.0)	38 (38.0)	<0.05
One	44 (44.0)	30 (30.0)		16 (16.0)	24 (24.0)	
Two	12 (12.0)	24 (24.0)		4 (4.0)	22 (22.0)	
Three	4 (4.0)	10 (10.0)		0	16 (16.0)	

Six months postoperatively, quality of life and tear film quality were significantly better in the FS-SMILE group compared with the FS-LASIK group. Worse scores of DED were found in FS-LASIK group $p < 05$ (Tables 2 and 3). Seventy six percent of patients in FS-SMILE group stopped using any eye drops at 6 months postoperatively compared to 52% in FS-LASIK group. No patients in FS-SMILE group needed any tear substitutes 6 months after surgery versus 18% of the FS-LASIK group who needed four times daily instillation of artificial tears even gels (Figure 1).

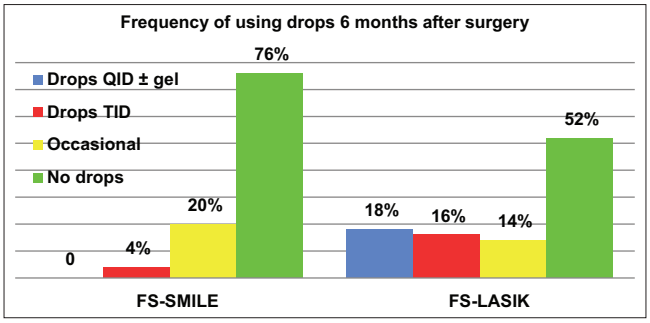

Figure 1: Tear eye drops used 6 months postoperatively in the two study groups

Corneal sensitivity postoperatively

Corneal sensitivity was reduced in both groups 1 month after the surgery, but FS-LASIK eyes showed lower sensitivity than FS-SMILE eyes ($p < 0.01$). Six months postoperatively, there was no statistical difference between the two groups, and both returned to normal, $p > 0.05$ (Table 4).

Table 4: Corneal sensitivity postoperatively as measured by the Cochete-Bonnet esthesiometer

Corneal sensitivity (cm)	Study group		P value
	SMILE	LASIK	
One month postoperatively	3.6 ± 1.8	2.3 ± 2.2	<0.01>0.05
Six months postoperatively	5.8 ± 0.2	5.6 ± 0.3	

Discussion

The present study was designed comprehensively regarding the approach to DED following the two refractive surgical modalities, demonstrating an increment in symptoms (OSDI score), and signs (TBUT) 6 months postoperatively in both FS-SMILE and FS-LASIK groups. Thus, there were lower values on these scales in patients treated with FS-Lasik compared to FS-SMILE for 6 months postoperatively, as some authors have reported [12], [13], [14], although ocular signs are often found to be highly variable, as pointed out by Feng *et al*. [6] Using a self-reported symptoms, questionnaire reported that 40% of the patients after LASIK believed that their eyes became dryer than before the surgery, Shah *et al*. [15] Recently, Li *et al*. [16] compared FS-Smile and FS-Lasik for ocular surface dryness and reported a better TBUT and OSDI in eyes treated with the former compared with eyes treated with the latter, also reported that the patients who had LASIK used eye drops more frequently for prolonged times, which might negatively affect the quality of life and the costs of these drops in this young population. In LASIK, flap creation and damage to sub-basal nerves contributes as a main, but not exclusively as a cause for ocular dryness. While, in SMILE procedures, more innervation in protected as it creates only a 40°–60° – wide penetrating corneal tunnel, in comparison to about 300° in LASIK. From the starting of refractive surgeries, studies had reported a significant decrement in CS following LASIK, which probably lasts for months or even years, even if the flap was created by femtosecond laser [17], [18], [19], [20], [21]. Recent clinical studies reported that SMILE preserved CS in comparison to LASIK [16], [22], [23], [24]. In the present study, CS significantly decreased compared to pre-operative values at 1 month postoperatively after LASIK, which went back to normal at 6 months in both groups, these were comparable to results of Demirok *et al*. [23].

Labbé *et al*. [25] reported that after 6 months, the CS was not different compared to healthy controls that suggest a stepwise recovery of the normal physiology in both procedures. In LASIK, there was reduced nerve density in the cornea over the long-term [17], [26], [27], while SMILE preserved the density as reported in the previous studies [8], [28].

The post-operative corneal reinnervation is highly variable, and the duration ranges from 3 months to 5 years according to different studies[29]. Another factor in LASIK might be the pathological increment in tear osmolarity, which seems not to occur in SMILE [29], [30], this might suggest that the post-operative dryness is usually a combination of neurogenic and inflammatory mechanisms [31].

Increased density of ocular surface dendritic cells was found 6 months after Lasik, which further support the role of inflammatory process in DED [8]. Tear cytokine measurement as inflammatory mediator could be better way for analyzes these inflammatory processes [31].

Epithelial thickness assessment by OCT at the center of the cornea did not show any difference between FS-SMILE and FS-LASIK groups 6 months post-operative. In the present study, bilateral surgery for each patient was performed using similar technique; thus, it was possible to perform inter-individual comparisons. Patients undergone LASIK or SMILE, which were matched and paired by age, gender, and refraction, this design might create a limitation compared with a paired-eye approach (one eye operated by SMILE and their fellow eye operated by LASIK). Good understanding of the pathogenesis involved in ocular dryness after corneal photorefractive surgery is a vital issue for two important reasons. First, to know the severity and impact of post-operative ocular dryness on quality of life and influenced the development of novel refractive procedures such as SMILE. Second, for determining the risk factors for post-operative DED and further comprehending the indications for each refractive procedure.

Limitations of the study

The present study reported significantly lower CS in the FS-LASIK group in comparison to the FS-SMILE group at 1 month following the surgery but not at 6 months, although some improvement to the outcomes of the study could be done by optimizing how to assess CS, like, incorporating a non-contact esthesiometer, and by recording the blinking rate and tear clearance, but the lack of appropriate equipment made it not possible. Other limitations were small sample size and the relatively short follow-up period of 6 months. The approach in the present study may be regarded as a limitation since the paired eye approach may be more disguised method for comparison, but it is not easily accepted by most patients.

Conclusions

This study demonstrated that FS-SMILE significantly decreased the incidence of ocular dryness disease in comparison to FS-LASIK in comparable samples postoperatively with normal pre-operative ocular surfaces. A time-dependent recovery of the normal ocular surface variables in the two procedures had been noticed 6 months' post-operative.

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