Effects of Warm Compress on Tear Film, Blink Pattern and Meibomian Gland Function in Dry Eyes After Corneal Refractive Surgery

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Research Article

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Abstract

Background

To assess the effects of warm compress (WC) on tear film lipid layer, blink pattern and Meibomian gland function in patients with dry eye following femtosecond laser small incision lenticule extraction (SMILE) and laser-assisted subepithelial keratomileusis (LASEK).

Methods

We enrolled 37 eyes of 37 participants, each with dry eye for more than 2 years following SMILE (25 eyes) or LASEK (12 eyes). WC was performed using a spontaneously heating eye mask. Safety parameters and effectiveness parameters (tear film break-up time, TBUT; tear film lipid layer thickness, TFLLT; blink pattern, and Meibomian secretory function scores, MGS) were assessed before and after WC.

Results

After WC, the following mean values all increased relative to baselines: central corneal thickness, spherical equivalent, minimum (Min-), maximum (Max-) and average (Ave-) TFLLT, TBUT, total MGS (TMGS), number of glands secreting any liquid (MGL), and complete blink rate (CBR) (p values ranging from < 0.0001 to 0.042). Partial blink frequency (PBF) and partial blink rate (PBR) decreased ($p = 0.002$ in both cases). The decrease of PBF was higher in SMILE subgroup than in LASEK ($p = 0.030$). TBUT variation was positively correlated with that of Ave-TFLLT and TMGS ($p = 0.046$, 0.028, respectively). Max-TFLLT variation was correlated with that of TMGS ($p = 0.020$).

Conclusions

WC may temporarily improve tear film quality and blink pattern, augment Meibomian gland function, and relieve dry eye symptoms after corneal refractive surgery, particularly that using the SMILE technique.

Background

With the incidence of myopia increasing globally,[1] keratorefractive procedures have gained widespread popularity in recent decades. With the benefit of novel techniques, especially the application of femtosecond laser in ophthalmology, keratorefractive procedures are now less invasive and safer, and correct refractive error more accurately than in the past.

Small incision lenticule extraction (SMILE) is the latest keratorefractive procedure. Modification of the corneal shape is achieved with a refractive stromal lenticule created using a femtosecond laser, with extraction through a small peripheral incision, refractive errors are thus corrected. [2] Laser-assisted subepithelial keratomileusis (LASEK) is a surface ablation procedure, which creates an epithelial flap only on the cornea. As both SMILE and LASEK avoid stromal flap creation, fewer corneal nerve fibers are severed, with concomitantly faster regeneration of the corneal nerves and recovery of corneal sensation relative to traditional laser-assisted in situ keratomileusis (LASIK) or femtosecond laser assisted LASIK (FS-LASIK). [3–5]

Nevertheless, as neural damage cannot be avoided completely, post-operative dry eye is still a common complication following SMILE and LASEK. Warm compress (WC) is effective for relieving the dry eye syndrome in healthy patients or those with Meibomian gland dysfunction. [6–7] Here, we employed a novel instrument for assessment of dry eyes to determine the effects of warm compress on tear film quality and Meibomian gland function as accurately as possible in post-operative patients.

Methods

Patients

Participants were recruited between July 2017 and October 2017 at the Department of Ophthalmology, Eye and ENT Hospital of Fudan University (Shanghai, China). The study adhered to the tenets of the Declaration of Helsinki and was approved by the Ethical Committee of the Fudan University Eye and ENT Hospital Review Board. All participants were fully informed and gave written consent for publication of this information.

We enrolled 37 right eyes of 37 participants (age 29.5 ± 6.3 years, 14 male and 23 female) who had experienced dry eye for more than 2 years following SMILE or LASEK. Among them, 25 underwent SMILE, and the remaining 12 underwent LASEK. All patients were routinely screened preoperatively and met the criteria for SMILE or LASEK, and all surgeries went smoothly and were performed by the same experienced surgeon (XTZ). We excluded patients who experienced new post-surgical severe ocular or systemic diseases or other long-term complications except dry eye.

Surgical procedures

We used the VisuMax femtosecond laser system (Carl Zeiss Meditec, Jena, Germany) to perform SMILE and the Mel-80 excimer laser system (Carl Zeiss Meditec AG, Jena, Germany) to perform was used to perform LASEK. We previously describe these procedures in detail. [8-9] The femtosecond laser settings were as follows: 500 kHz repetition rate, 130 nJ pulse energy, 110 to 120 μm intended cap thickness, 6 to 6.5 mm optical zone, 7.3 to 7.5 mm cap diameter, and a 2 mm side cut at the 12 o’clock position.

Clinical examinations

Safety and effectiveness parameters were assessed sequentially before and at 5 min after WC. Safety parameters: corneal curvature (K1, K2, Km) and central corneal thickness (CCT) measured by Pentacam HR (Oculus GmbH, Wetzlar, Germany), uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA) and spherical equivalent (SE). Effectiveness parameters: tear film lipid layer thickness (TFLLT), blink frequency, Meibomian secretary function scores, and tear film break-up time (TBUT). All patients were instructed to stop using eye drops such as artificial tears or wearing contact lenses 24 hours before examinations, and to avoid skin care products or make-up around the eyes. All examinations were performed between 11:00 am and 17:00 pm in the same room by a single pre-trained and experienced technician. The indoor temperature was set to 22 - 25 °C.

TBUT was measured using fluorescein sodium solution and a digital clock. The averages of three repeated measurements were recorded as final values.

Warm compress

All patients were treated for 20 minutes with a warm compress using a spontaneous heating eye mask (Zhenshiming Pharmaceutical Co., Ltd, Fuzhou, Jiangxi, CHN) according to the manufacturer's instruction. This eye mask is a standardized, fragrance free, over-the-counter eyeshade, certified after examination and verification by Shanghai Institute of Quality Inspection and Technical Research. At an ambient temperature of 25 ± 2 °C, it takes an average of 3 min to warm up to 35 °C, and maintains temperature over 35 °C for an average of 30 min. The mean temperature was 40.7 °C.

LipiView

An interferometer (LipiView, TearScience® Inc, Morrisville, NC) was used for measuring the quantitative TFLLT and blink frequency dynamically by analyzing more than one million tear film data points. TFLLT was calculated using interferometry color described as interferometric color units (ICUs), which is equivalent to 1 nanometer (nm). Patients were instructed to hold their head in a comfortable position and look directly into the camera without deviation of eye position, and to blink freely throughout imaging. Natural light from the source passed through the tear film and was reflected back to the camera. The measurement region was the lower third of the cornea, approximately 1 mm above the inferior tear meniscus. The minimum (Min-), maximum (Max-), average (Ave-) and standard deviation (-std) TFLLT were analyzed automatically within preset 19.1 s. Simultaneously, total (TBF) and partial blink frequency (PBF) were also recorded, and were used to calculate partial blink rate (PBR) and complete blink rate (CBR). The upper cut-off of LipiView is 100 ICU; values higher than this are recorded as 100+ ICU. A conformance factor for imaging ≥ 0.7 was considered acceptable, but to ensure quality of our data, only conformance factor ≥ 0.8 were included in the final analysis.

Meibomian gland evaluator

Secretory function of the Meibomian glands was measured by a handheld Meibomian Gland Evaluator (TearScience® Inc, Morrisville, NC) and recorded as Meibomian gland scores. Gentle and blink-stimulated pressure (0.8 g/mm^2 - 1.2 g/mm^2) was applied to the Meibomian gland openings along the lower eyelid margin. The width of the evaluator covers an average of 5 gland openings. After gentle clean of the lower eyelid using clean cotton swabs, the evaluator was applied 1-2 mm below and in parallel with the eyelid, near the root of the eyelash. The eyelid was gently turned inside out slightly just until the gland opening was clearly visible. Fifteen glands in 3 regions (temporal, central, and nasal) were evaluated, with an average pressing time of 10-15 seconds. We graded the number and secretion characteristics of glands: 3 points (clear liquid), 2 points (cloudy liquid), 1 point (toothpaste-like), and 0 (no secretion). The following metrics were calculated: the total Meibomian gland secretion score (TMGS) of all 15 glands, ranging from 0 to 45; the number of glands secreting any liquid (MGL, clear or cloudy liquid, grade 2 or 3); and the number of glands secreting clear liquid (MGC, clear liquid, grade 3).

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS ver. 22.0 (SPSS Inc, Chicago, IL, USA). Variables were described as averages ± standard deviations. The one-sample Kolmogorov-Smirnov test was used to test for normality. Paired t-tests or Wilcoxon tests were then used to analyze the changes from baseline in normal or non-normal distribution parameters, respectively. Variables were compared between SMILE and LASEK using independent sample t-tests or Mann-Whitney U tests. Pearson or Spearman correlation analyses were used to evaluate the linear relationships between different variables. $P < 0.05$ was considered statistically significant.

Results

No adverse events were observed during the study. Before WC, no difference of safety or effectiveness indicators were observed between surgeries.

Safety Outcomes

After WC, the mean SE value and CCT increased significantly (p=0.042, 0.006, respectively), while UDVA, CDVA, K_1, K_2, K_m, total higher order aberrations (HOAs), Z (4, 0), Z (3, 1) and Z (3, -1) remained unchanged (p>0.05) (Table 1). The increased CCT was significant in eyes following LASEK (P=0.021), but not in eyes following SMILE (p=0.072). Beyond that, no significant differences of other safety parameters were observed within either subgroup or between surgeries.

TFLLT

The mean values of Min-, Max- and Ave-TFLLT increased significantly after WC (p<0.001, p=0.023, p<0.001, respectively, Figure 1A), whereas TFLLT-Std did not change. Figure 2 shows the contrast image under the LipiView display window before and after WC. Significant increases of Ave-, Max- and Min-TFLLT were observed in postoperative eyes in the SMILE group (p<0.001, p=0.006, p<0.001, respectively), but only Ave- and Min-TFLLT increased significantly following LASEK (p=0.006 and 0.015, respectively). No significant difference was observed between surgeries. (Figure 3A)

Blink Pattern

Both PBF and PBR decreased significantly after WC (p=0.002 in both cases, Figure 1B, D). Following SMILE, significant decreases were observed in PBF (p<0.001) and PBR (p=0.008), whereas an increase was observed in CBR (p=0.012). There was no significant change in the LASEK subgroup. With the exception of PBF (p=0.030), there was no significant difference between surgeries. (Figure 3B, D)

TBUT and Meibomian Gland Function

The mean TBUT value increased significantly from 5.38 ± 2.19s to 6.38 ± 2.16s (p<0.001). The differences were significant in both SMILE (5.65 ± 2.12s to 6.26 ± 1.51s, p=0.009) and LASEK (4.82 ± 2.32s to 6.64 ± 3.20s, p=0.008) subgroups, but not between surgeries. There were statistically significant increases in TMGS and MGL (p=0.002, 0.004, respectively), but not in MGC (Figure 1C). Significant increase of TMGS (p=0.011) and MGL (p=0.014) was observed in SMILE subgroup, whereas not in LASEK subgroup or between surgeries (Figure 3C).

CORRELATION ANALYSIS

The change in TBUT (△TBUT) was positively correlated with △Ave-TFLLT (Figure 4A) and △TGMS (Figure 4B). △Max-TFLLT was positively correlated with △TMGS (Figure 4C). After adjustment for age, sex and pre-operative SE, △TBUT was still positively correlated with △TMGS (Figure 4B), also with △MGL (r=0.649, p=0.001), △MGC (r=0.604, p=0.004) and △TBF (r=0.487, p=0.025). △Max-TFLLT was still positively correlated with △TMGS (Figure 4C), and △Ave-TFLLT was positively correlated with △PBF (Figure 4D).

Discussion

Dry eye syndrome is one of the most common postoperative complications of corneal refractive surgery (CRS), usually presenting as a transitory phenomenon during the early stages of recovery that naturally resolves several months later. However, complaints of persistent dry eye symptoms cannot be ignored in clinical practice. CRS was reported to be a risk factor for dry eye,[10] which in turn increased the risk of refractive regression postoperatively.[11] It is therefore very important to improve the postoperative prognosis and break this vicious cycle by relieving chronic dry eye after CRS.

Among the different tear layers, the outer lipid layer is thought to retard evaporation and increase stability of the tear film. Changes in distribution and decreased thickness of this layer can lead to dry eye,[12] and TFLLT is significantly correlated with other dry eye indicators.[13] As a newly invented ocular surface interferometer, LipiView permits dynamic measurement of the lipid layer thickness with simultaneous recording of the blink pattern. The efficacy and repeatability of this instrument has been previously confirmed, [14-15] and it has been used in the evaluation of dry eye,[16] Meibomian gland dysfunction[17] and post-cataract surgery[18]. The repeatability and accuracy of TFLLT measurements with LipiView are superior to another commonly used instrument (Keeler Tearscope-Plus™).[15]

This study showed significant increases in TFLLT and TBUT after WC, and improvements in Meibomian gland function. These results agree with previous studies of patients with long-term dry eye after CRS.[19] One possible explanation is that WC contributes to dilating the Meibomian gland ducts, melting meibum and promoting liquid secretion and thus further reducing the evaporation of tears, and increasing the stability of the tear film. Jung et al reported deterioration of Meibomian gland structure and function in CRS patients following surgery relative to healthy individuals, and found surgical history to be negatively correlated with gland performance measures.[20] This being so, it is reasonable to assume that WC will confer greater benefits on postoperative patients than on healthy individuals, a possibility that warrants further investigation. Besides, we observed significant increases in TMGS and MGL but not in MGC, suggesting that the improvement occurred mainly in dysfunctional Meibomian glands by reducing obstruction rather than stimulating secretion.

The increased Ave-TFLLT and Min-TFLLT values were both higher than the upper limits of the deviations for previously repeated measurements (from -9 to 16 nm),[14] indicating a significant change. The smaller variations of Max-TFLLT relative to Ave-TFLLT and Min-TFLLT may result from limitations of the measurement capability of the former by the LipiView detection range (up to 100 nm), particularly in patients with high Max-TFLLT baseline values. It is worth noting that the dry eye was more prevalent in Asian populations than Australian populations.[21-22] Moreover, the risk of chronic dry eye after refractive surgery was also significantly higher among Asians,[23] suggesting the possibility of ethnic differences in dry eye. Mean Ave-TFLLT was recently measured at 54 nm among Asians,[14] which seems significantly lower than previous report in dry eye patients (76 ± 25 nm).[24] Given that Meibomian gland disease was also more common among patients with low TFLLT (≤ 60 nm),[24] clinicians attending Asian patients should be aware of the risks of post-operative dry eye problems.

Blinking is important for promoting the secretion of lacrimal gland, recoating the cornea with tears, and maintaining good visual acuity. Decreased blinking frequency is an important factor contributing to postoperative tear film instability,[23,25] but the effectiveness of blinking is often overlooked in clinical practice. In our study, both PBF and PBR decreased significantly after WC, indicating improved blink efficiency. TRF appeared unaffected both by WC and by other variables that we measured. It is reasonable to assume that relative to total blinking, partial blinking might have a bigger impact on long-term tear film stability. This conjecture was supported by a previous study, which indicated that extent of blinking rather than total blink rate was the determinant for tear film instability.[26] A possible explanation is that incomplete blinking may cause defects in re-distribution of the mucin and lipid layers, thereby increasing tear evaporation and decreasing lipid layer thickness. Moreover, the impaired corneal innervation and reduced protective blink reflex following CRS may increase partial blinking rate and tear film instability.[27] It is particularly noteworthy that the blinking habit is trainable, and blink efficiency exercises can achieve long-lasting benefits.[27-28] Methods to modify blinking habits and reduce partial blinking are therefore worth exploring for postoperative patients with chronic dry eye.

We show that variation in TBUT was positively correlated with that of TFLLT and Meibomian gland scores, and the latter two parameters were also positively correlated. After adjustment, the variation in PBF was positively correlated with Ave-TFLLT. These results agree with previous studies[16,25] suggesting that TFLLT, Meibomian gland score and blink pattern might be effective evaluation indices for tear film stability, similar to the traditional indicator TBUT.

To further compare benefits between the two surgery types, we analyzed the effects of WC on SMILE and LASEK patients. There was no significant difference between two groups before WC. After WC, TFLLT-Max, CBR and Meibomian gland function improved significantly in the SMILE group, whereas PBF and PBR decreased. No significant changes of any above indicators were observed in the LASEK group, indicating that different surgical procedures may differ in their impact on the recoverability of TFLLT and blink pattern. However, there was no significant difference between the two groups except PBF, suggesting that assessment of this possibility awaits further investigations with larger sample sizes.

To assess the safety of this treatment, we measured vision, keratometry, corneal thickness, and aberration but observed no significant differences in most safety parameters before and after WC. Solomon et al reported blurred vision and decreased visual acuity after WC.[29] Interestingly, the slight but significant decrease we observed in SE was the opposite of that. Different WC methods and measurement sequences among studies may account for this discrepancy. For example, vision measured immediately after WC might be blurred. At present study, WC went smoothly without adverse effects or complaints of discomfort, demonstrating that short-term WC was safe for post-CRS patients.

There are some limitations to our study. First, we should have included corneal sensation and intraocular pressure among our effectiveness and safety parameters, given that decreased corneal sensation may be associated with tear secretion and blink status, and intraocular pressure change has been observed after WC.[30] Second, this study only focused on lipid layers and not on other tear components. Third, there is currently no reference standard for duration, frequency and temperature of WC, so we followed the manufacturer's instructions. Moreover, we recommend using an infrared thermometer along with the WC device, for even temperature maintenance and accurate temperature record. Fourth, LipiView only measured the lower part of the cornea and we therefore lacked information about overall corneal condition. This may have increased the likelihood that our analyses exaggerated the role of incomplete blinking on tear thinning, because the consequences of such blinking are localized on the inferior cornea.[28] Lastly, this study focused exclusively on changes immediately after WC; studies over a longer time scale and regular WC sessions are needed as a follow-up.

Conclusion

In conclusion, our study demonstrated that warm compress may also relieve postoperative dry eye syndrome, especially in those underwent SMILE procedure. Several possible mechanisms may be involved in this result, including improvement of tear film quality, blink pattern and Meibomian gland function.

List Of Abbreviations

WC, warm compress; SMILE, femtosecond laser small incision lenticule extraction; LASEK, laser-assisted subepithelial keratomileusis; LASIK, laser-assisted in situ keratomileusis; FS-LASIK, femtosecond laser assisted laser-assisted in situ keratomileusis; TBUT, tear film break-up time; TFLLT, tear film lipid layer thickness; MGS, Meibomian secretory function scores; Min-, minimum; Max-, maximum; Ave-, average; TMGS, total Meibomian secretory function scores, MGL, number of glands secreting any liquid; TBF, total blink frequency; MGC, number of glands secreting clear liquid; CBR, complete blink rate; PBF, Partial blink frequency; PBR, partial blink rate; CCT, central corneal thickness; UDVA, uncorrected distance visual acuity; CDVA, corrected distance visual acuity; SE, spherical equivalent; ICUs, interferometric color units; std, standard deviation; HOAs, higher order aberrations; CRS, corneal refractive surgery

Declarations

Ethics approval and consent to participate: This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Eye and ENT Hospital Review Board of Fudan University. Written informed consent was obtained from all patients after the nature and possible consequences of the study were explained.

Consent for publication: All participants in this study signed written consent forms for the publication of their relevant clinical data.

Availability of data and material: Data and materials are available upon request from the corresponding author at doctzhouxingtao@163.com.

Competing interests: The authors declare that there is no competing interest.

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Authors’ Contributions: XYZ, YS and XTZ: designed study; XYZ, YS, JS: conducted study; XYZ, JS: collected data; XYZ, YS: analyzed and interpreted data; XYZ, wrote the main manuscript text; XYZ, prepared figures and table; all authors reviewed the manuscript; XTZ: final approval of article.

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Tables

Table 1 Overall differences of safety indicators from before to after warm compress (WC)

	Pre-WC	Post-WC	p value
Visual parameters			
LogMAR UDVA	-0.05±0.10	-0.08±0.09	0.270
LogMAR CDVA	-0.12±0.07	-0.13±0.07	0.317
SE (Diopter, D)	-0.47±0.52	-0.34±0.42	0.042*
Corneal Keratometry			
K1	38.55±2.19	38.59±2.22	0.953
K2	39.44±2.12	39.45±2.19	0.899
Km	38.99±2.15	39.02±2.19	0.816
CCT (um)	462.47±44.03	471.57±49.01	0.006*
HOAs			
Total HOAs	0.63±0.51	0.85±0.38	0.593
Z (4, 0)	0.30±0.27	0.39±0.23	0.970
Z (3, 1)	-0.13±0.34	-0.15±0.34	0.101
Z (3, -1)	-0.43±0.46	-0.42±0.44	0.688

All data are expressed as the mean ± standard deviations (μm).

UDVA, uncorrected distance visual acuity; CDVA, corrected distance visual acuity; SE, spherical equivalent; CCT, central corneal thickness; HOAs, higher order aberrations.

*Significant difference

Figures

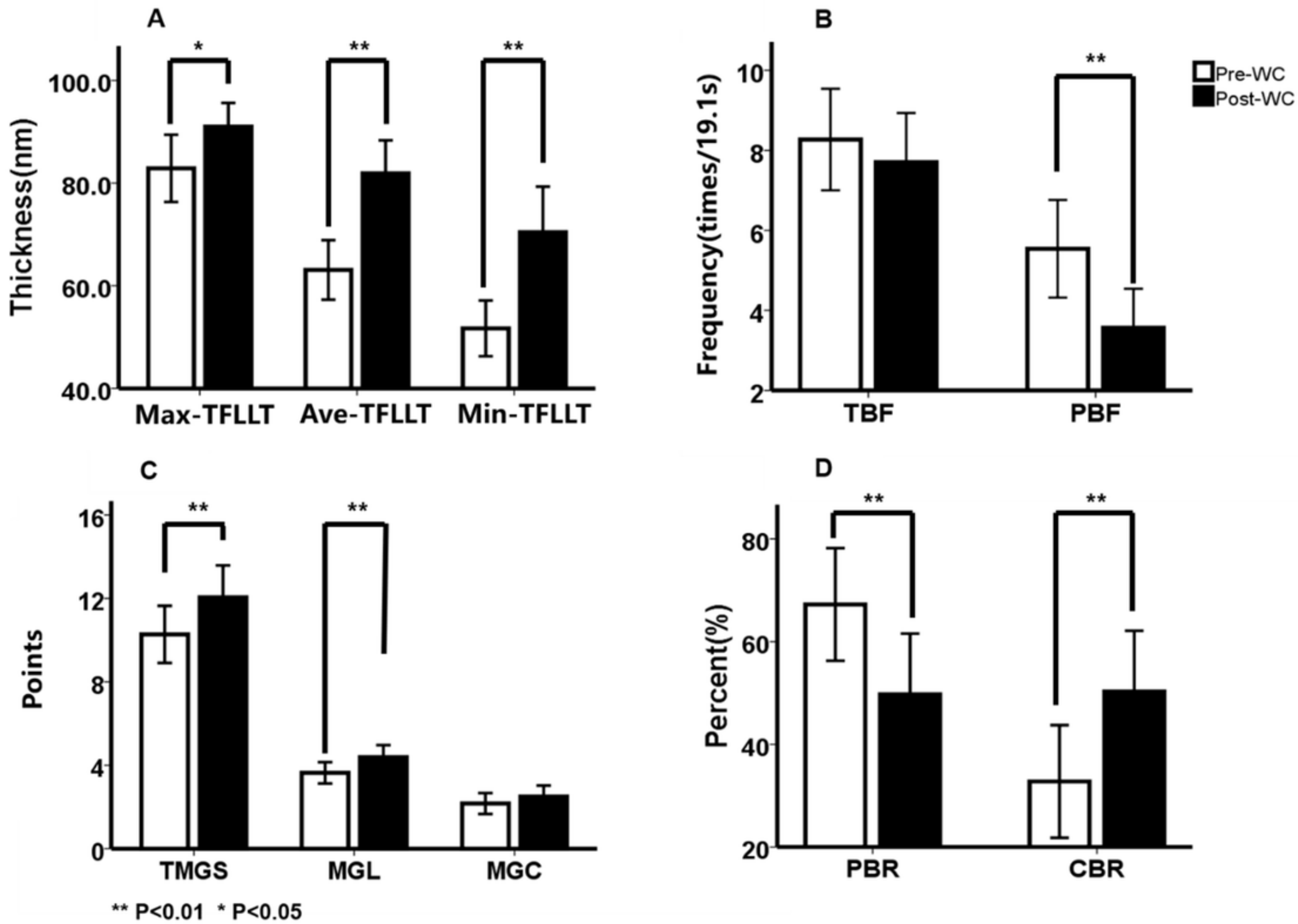

Figure 1

Change in TFLLT, blink frequency, meibomian glands scores and blink rate after WC. (A: Min-, Max- and Ave-TFLLT; B: total and partial blink frequency; C: different meibomian glands scores; D: complete and partial blink rate).

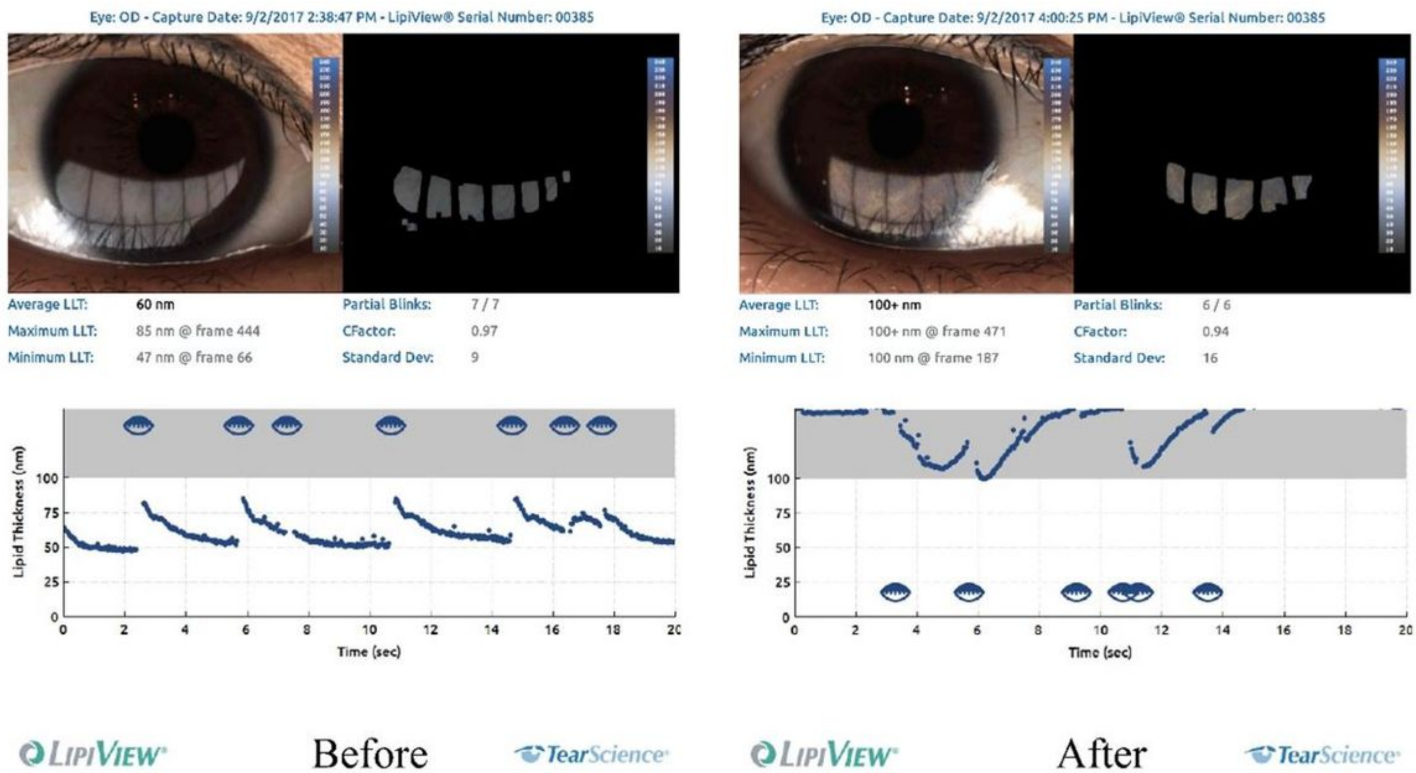

Figure 2

Interference pattern of a patient before (A) and after (B) warm compress under LipiView inspection window.

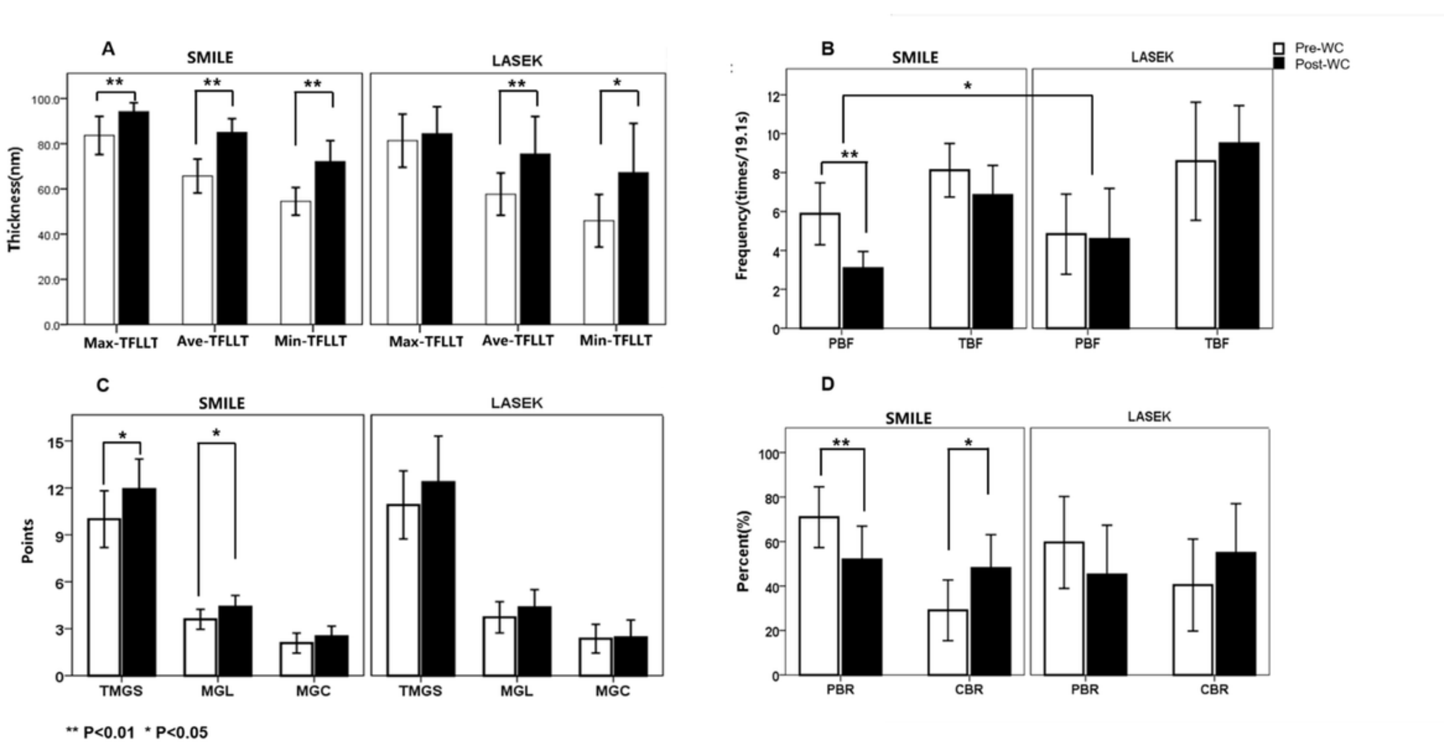

Figure 3

Change in TFLLT, blink frequency, meibomian glands scores and blink rate after WC following SMILE and LASEK. (A: Min-, Max- and Ave-TFLLT; B: total and partial blink frequency; C: different meibomian glands scores; D: complete and partial blink rate).

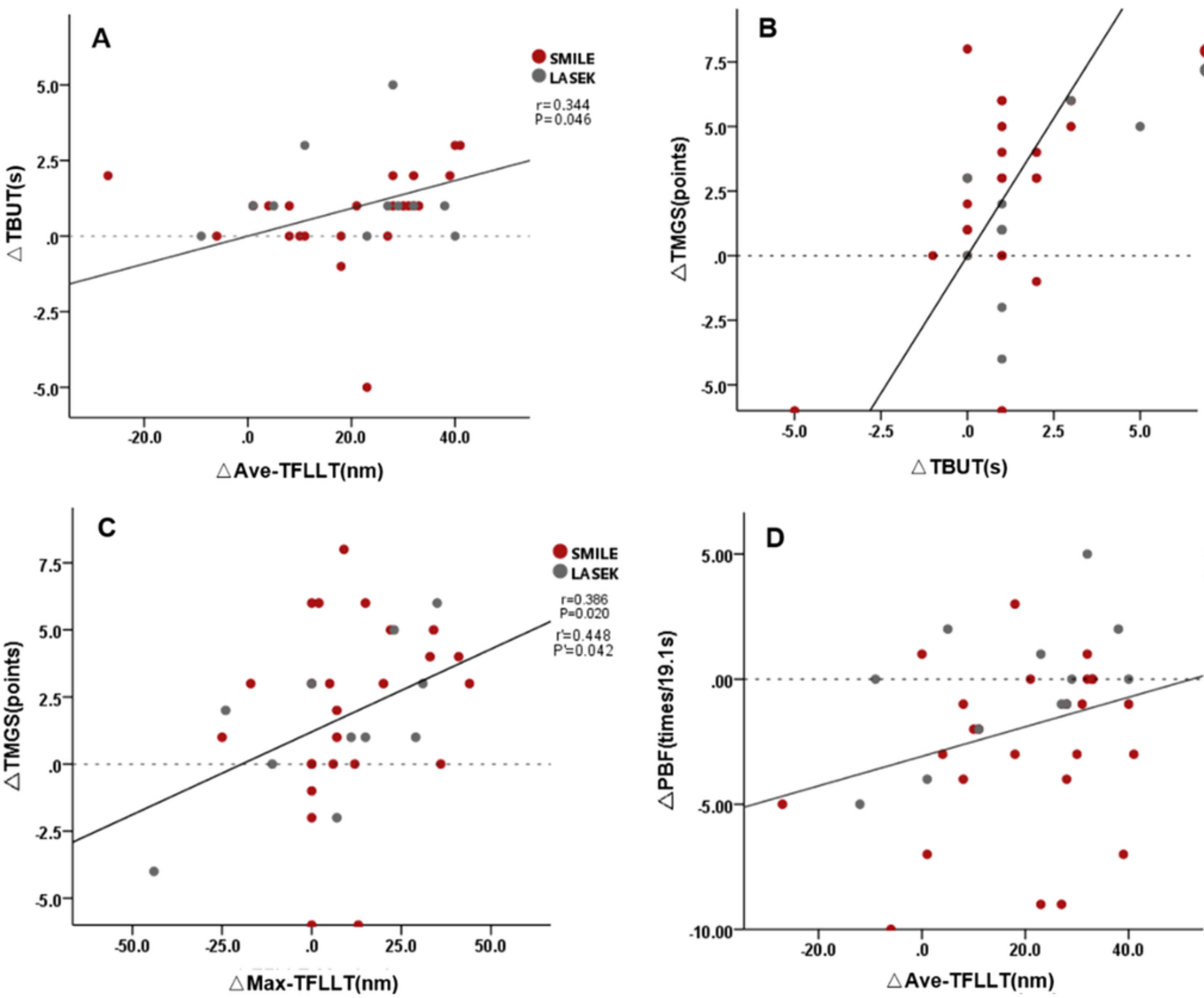

Figure 4

Correlations between different variations. R or P-value with superscript indicates result after adjustment for age, sex, and pre-operative SE.