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Perioperative intense pulsed light to prevent and improve symptoms of post-laser corneal refractive surgery dry eye. A randomized clinical trial

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ABSTRACT

Purpose: To evaluate the efficacy of perioperative IPL therapy in preventing postoperative ocular surface disorders in patients undergoing corneal laser refractive surgery.
Design: randomized, controlled, clinical trial with triple-blinding.
Methods: Setting: Vissum Miranza - Alicante; *Study population*: 61 patients randomized in two groups: 31 study patients (perioperative IPL + laser refractive surgery) and 30 control patients (perioperative placebo + laser refractive surgery). Follow-up was conducted over a 6-month period; *Intervention:* Each participants underwent three IPL sessions with a two-week interval between each session (pre-surgery, post-surgery week-one, and post-surgery week-three). For controls, placebo was administered following the same protocol. *Main outcomes measures*: visual outcomes and refraction, slit-lamp examination, corneal topography, visual analogue scale questionnaire and Oculus Keratograph 5 M including tear meniscus height, non-invasive tear break- up time, ocular redness, infrared meibography and Ocular Surface Disease Index (OSDI) questionnaire.
Results: 61 randomized eyes were included. No significant differences were observed in terms of uncorrected and corrected distance visual acuity (UDVA, CDVA), refractive error or corneal aberrations. A statistically significant improvement in OSDI score (change −8.47, $p = 0.043$), tear meniscus (change 0.05 mm, $p = 0.004$) and Meibography (change −0.42, $p = 0.012$) was observed at the third postoperative month in the study group. Additionally, at the sixth postoperative month, there were statistically significant improvements in tear meniscus (change 0.06 mm, $p = 0.018$), tear break-up-time (change 1.68 s, $p = 0.039$) and Meibography (change −0.37, $p = 0.030$).
Conclusions: Results suggest that perioperative IPL therapy applied to laser corneal refractive surgery improves objective and subjective ocular surface parameters over non-IPL-treated control patients and early postoperative dry eye symptoms.

Introduction

Corneal laser refractive surgery has a transient negative impact on the ocular surface and tear film, which may lead to the development of dry eye syndrome (DES) in certain patients.[1] In turn, DES may alter corneal curvature, refractive power, and produce irregularities on the ocular surface inducing a decrease in visual acuity and retinal image quality.[2,3]

DES after laser refractive surgery is a multifactorial disease affecting the corneal surface.[4,5] Its pathophysiology involves several mechanisms, with corneal denervation being one of the main causes (results from the sectioning of anterior stromal nerves during the ablative procedure).[6] This denervation leads to reduction in corneal sensitivity, reducing tear production by the lacrimal glands as well as the reduction of blink reflex, ultimately resulting in reduction in the secretion rate of the meibomian glands, which then contribute to meibomian gland dysfunction (MGD). Moreover, corneal laser refractive surgery triggers an increase in inflammatory cytokines[7] and reduces mucin production[8] by the corneal epithelium and goblet cell density, which further exacerbates MGD.[9] For this reason, it is crucial to consider strategies that could mitigate the negative impact of corneal laser refractive surgery in the ocular surface.

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In recent years, the use of Intense Pulsed Light (IPL) therapy has gained popularity as a treatment for evaporative dry eye associated with MGD. IPL therapy improves dry eye symptoms through a range of mechanisms[10], including the destruction of superficial blood vessels, leading to reduction in local inflammation. Additionally, it can also aid the liquefaction of meibum, and provide antimicrobial, anti-inflammatory, and antioxidant effects, which further contribute to the overall improvement of dry eye symptoms.

Published studies have analyzed IPL therapy in patients with a prior diagnosis of MGD.[11] More recent prospective studies have also evaluated its postoperative use in patients following laser-assisted in situ keratomileusis (LASIK) surgery, with successful outcomes observed in patients up to 10 years post-surgery.[12,13] Furthermore, IPL therapy has also been examined as a preoperative treatment in cataract surgery[14]. However, despite these findings, there is currently a lack of research examining the use of IPL therapy as a preventative treatment of ocular surface disorders in healthy population undergoing laser corneal refractive surgery.

So far, most efforts to manage dry eye associated with refractive surgery have focused on treating its aqueous-deficient component, but not the evaporative component. Given that all forms of laser corneal refractive surgery impact the ocular surface and exacerbate MGD, it is reasonable to consider the use of perioperative IPL as a prophylactic therapy for ocular surface disorders.

The aim of the present study was to set a randomized and masked clinical trial to elucidate the value of perioperative IPL therapy for the prevention of postoperative ocular surface disease in patients undergoing lamellar corneal laser refractive surgery such as small-incision lenticule extraction (SMILE) and femtosecond laser-assisted in situ keratomileusis (FS-LASIK).

Methods

This is a randomized, controlled and triple-masked clinical trial conducted in Vissum (Miranza Group, Alicante, Spain). Study participants were randomized in two groups: study group (perioperative IPL + laser refractive surgery) and control group (perioperative placebo + laser refractive surgery). The study adhered to the tenets of the Declaration of Helsinki and received approval from the Institutional Review Board (IMO201106_156) of the Eye Microsurgery Institute. It was officially registered at clinicalTrials.gov (NCT05139511). All patients provided written informed consent prior their inclusion.

Recruitment was performed by consecutive probabilistic sampling with randomization stratified by type of surgery (FS-LASIK vs SMILE) between 2021 and 2023. All refractive surgeries were performed by the same experienced surgeon (J.A.B) following a standardized protocol. The VisuMax 500 kHz femtosecond laser system (Carl Zeiss Meditec AG) was utilized for LASIK and SMILE procedures. The Amaris 750 excimer laser (Schwind eye-tech-solutions) was employed for LASIK excimer ablations. IPL treatment was performed exclusively by two experienced ophthalmologists (M.M.H; M.A.A). [15] Treatments were performed with the M22 Optima IPL (Lumenis, Israel) and the parameters were adjusted to the appropriate setting according to Fitzpatrick skin classification. Therapy started 7 days before the refractive procedure, with a total of 3 IPL sessions with a two-week interval between each session. Therefore, IPL sessions were applied 7 days before, 7 days after and 21 days after surgery. Blinding of patients in the control group was performed using an IPL protocol identical to that of the experimental group, but without the use of energy. All measurements were collected by a masked observer who did not know the group assigned to the patients.

Inclusion and exclusion criteria

Inclusion criteria included: (1) age of at least 18 years, (2) patient suitable for laser corneal refractive surgery; (3) skin Fitzpatrick scale I-IV.[16]

Exclusion criteria were: (1) pregnancy or lactation; (2) skin Fitzpatrick scale V-VI (3) piercings over the treated zone; (4) personal history of autoimmune diseases, epilepsy, prior herpes, suspicious skin lesions or photosensitivity; (5) acute intraocular inflammation; (6) personal history of infectious blepharitis, vernal or atopic keratoconjunctivitis, previous eye trauma or surgery, or alterations of the palpebral margins; (7) treatment in the previous month with systemic or topical corticosteroids, oral or topical antihistamines, topical vasoconstrictors, medication with anticholinergic activity or photosensitive drugs; (8) patient unsuitable for laser corneal surgery due to pre-existing ocular surface disease, unsuitable topographic or insufficient corneal thickness.

Surgical technique

SMILE procedure: circle pattern with a pulse energy of 120 nJ and spot spacing of 3.8 μm. The lenticule diameter was adjusted to the scotopic pupil size, with an optical zone up to 7.0 mm and a standard diameter of 6.5 mm. Minimal lenticule thickness was set to 15 μm, and the targeted cap thickness was 120 μm. The lenticule was extracted through one 2.3 mm anterior side cut.

FS-LASIK procedure: circle pattern with a bed energy of 200 nJ, and a spot and line separation of 4 μm, resulting in a targeted flap thickness of 110 μm with 9.0 mm diameter. The excimer ablation was programmed to create a total ablation zone that matched or exceeded the scotopic pupil size.

A regimen of standard antibiotic and anti-inflammatory eye drops were applied in both procedures.

IPL therapy procedure (Fig. 1): (Step 1) double pass technique of 12 impacts on the infraorbital/lower eyelid region with a 15 × 35 mm guide light; (Step 2) simple pass technique of 6 impacts over the lower eyelids with a 6 mm cylindrical guide light; (Step 3) and a double pass technique of 3 impacts over the upper eyelids with a 8 × 15 mm guide light. Energy and guide-light wavefront filters were adjusted according to Fitzpatrick skin classification (Table 1). For this study, we did not use a corneal surface protector or perform meibomian gland expression after IPL, as we considered its use to be a risk of trauma to the flap and cap during the immediate postoperative period. The effectiveness and safety of this technical modification of periocular and eyelid IPL has been published in a recent study by our group[15] where no adverse effects were reported, thus proving its direct application at low energies without the use of a corneal surface protector as safe. For the control group, placebo was administered following the same treatment protocol and visit schedule. But in this case, the wavelength was filtered through an opaque medium that prevented the use of energy.

Clinical assessment

Data collection before and at 1-day, 1-week, 1-month, 3-months and 6-months after surgery included: (1) visual outcomes; uncorrected and corrected distance visual acuity (UDVA, CDVA) and manifest refraction; (2) Slit-lamp examination (ocular surface, corneal or eyelid abnormalities, Oxford scale of corneal fluorescein staining,[17] lens health and fundus examination); (3) Corneal topography and corneal wavefront aberrations (MS-39; CSO, Italy); (4) Visual Analogue Scale (VAS) questionnaire; and (5) Oculus Keratograph 5 M (K5M) (Oculus, Wetlzar, Germany) with Jenvis dry eye report (Jenvis Research Institute, Jena, Germany) including: (a) tear meniscus height (TM) analyzed in millimeters; (b) non-invasive tear break- up time (NI-TBUT) analyzed in seconds; (c) ocular redness according to the Jenvis grading scale manufacturer; (d) upper and lower infrared meibography (IM); (e) Ocular Surface Disease Index (OSDI) questionnaire.[18]

Ocular redness was quantified based on the area percentage ratio between the vessels and the rest of the analyzed area, with the maximum ratio, according to the manufacturer of 4, so consider 1 as normal redness (0–1.5); 2 as mild redness (1.6–2.5); 3 as moderate (2.6–3.5) and 4 as severe (3.5–4).

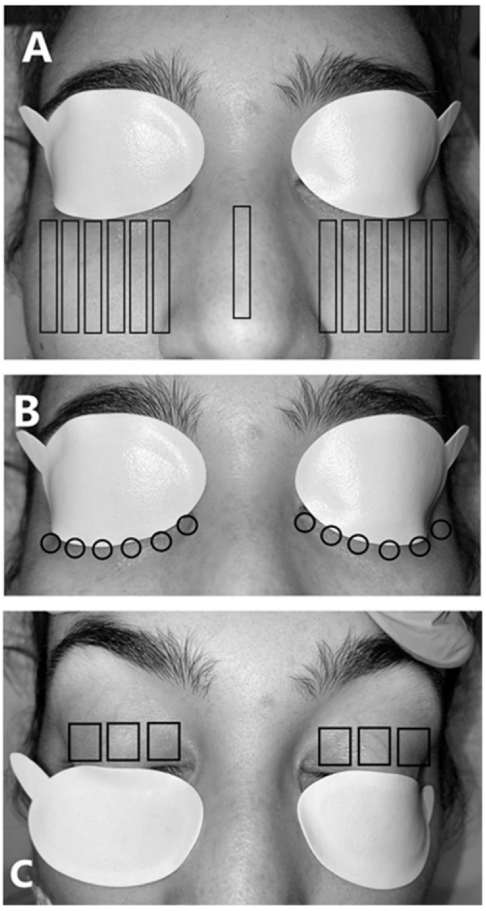

Fig. 1. IPL protocol. (A) Step 1. (B) Step 2. (C) Step 3.

Infrared meibomian glands were analyzed according to the degree of loss on the Jenvis grading scale: 0 for no loss; 1 for a loss under 33%; 2 for a loss between 33% and 66%, and 3 for a greater loss and the final score is shown as an average of upper and lower eyelids.

Statistical analysis

A random number sequence (dichotomic sequence 0 and 1) was created using computer software by the study statistician. Based on the sequence, patients from Vissum Miranza candidate to Smile and IntraLasik surgeries were treated with IPL (1) or with Placebo (0). All data was analyzed using IBM SPSS Statistics for Windows version 26.0. The sample size was calculated based on the NI-TBUT, accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test. This calculation resulted in a requirement of 25 subjects per group to detect a difference equal to or greater than 4 s, assuming a common standard deviation of 5 s and a drop-off rate of 10%. Computer software generated a dichotomic (0 and 1) random number sequence to selectively choose data from one eye per patient to adjust the effect of the correlation between fellow eyes on outcomes. Descriptive statistics were expressed as means, standard deviations, medians, and interquartile range. After testing the normality of the variables with the Kolmogorov–Smirnov test, the Mann-Whitney U test was conducted to compare variables pairwise. Comparisons were also made by using generalized estimating equation models (GEE) to adjust for any correlation between fellow eyes of the same patient.[19] Data before and after IPL was compared using the Wilcoxon signed-rank test. Statistical differences were set at $p < 0.05$ and effect size was calculated using Cohen's D, assuming moderate effects ranging from 0.5 to 0.7 and large effects of 0.7 or greater.

Results

Sixty-one patients (33 females and 28 males) were included in the clinical trial (mean age: 32.90 ± 7.60 years and Spherical Equivalent (SE) − 2.60 ± 3.57). Thirty-five received FS-LASIK (18 study patients and 17 control patients) and 26 received SMILE (13 study patients and 13 control patients). The mean age of the experimental group was 32.94 ± 7.12 years and SE − 2.74 ± 3.22 and the mean age of the control group was 32.87 ± 8.19 and SE − 2.45 ± 3.95. There were no statistically significant differences in age ($p = 0.965$) or SE ($p = 0.767$) between the study and control group. All patients completed the 6-month follow-up and no complications from either the IPL treatment or the surgical procedure were reported.

In a preliminary evaluation, we compared the ocular surface outcomes between FS-LASIK and SMILE patients (Table 2), no significant differences between both techniques at any of the study visits were observed. This finding is in accordance with previous literature, where there were no clinical differences in objective signs or subjective symptoms of ocular surface disease between both techniques.[20–27] Therefore, study and control groups were analyzed considering both techniques together (SMILE and FS-LASIK) and not stratifying according to the surgical technique applied.

Visual, refractive and aberrometric outcomes

No significant differences were observed in terms of UDVA, CDVA, refractive error or corneal aberrations (Table 3) between the study and control groups along the entire follow-up, except for the SE at third month ($p = 0.022$).

Ocular surface outcomes

The ocular surface outcomes were evaluated subjectively by slit lamp examination and patient questionnaires, and objectively using the Keratograph 5 M (Table 4 **&** Fig. 2).

Table 1
Parameters used according to Fitzpatrick classification.

Fitzpatrick skin	Wavelength filter (nm)	Fluence (J/cm2)	Pulses	Duration (ms)	Delay (ms)
Cheek-Nose					
I	560	20	Triple	3	15
II	560	19	Triple	3	20
III	560	18	Triple	3	25
IV	590	17	Triple	3	30
Lower eyelids					
I-IV	590	16	Triple	6	50
Upper eyelids					
I	590	11	Triple	6	50
II	590	11	Triple	6	50
III	590	10	Triple	6	50
IV	590	10	Triple	6	50

Table 2
Statistical analysis of variables over time for FS-LASIK vs SMILE. The data are presented as means, standard deviations and means change with 95% confidence interval. VAS: visual analogue scale; OSDI: Ocular surface disease index; TM: tear meniscus; NI-TBUT: non-invasive tear break-up-time; IM: infrared meibography.

Dry eye outcomes VAS	Pre	1 M	3 M	6 M
FS-LASIK	5.83 ± 10.10	8.48 ± 12.10	4.83 ± 9.65	4.91 ± 8.03
SMILE	7.51 ± 8.22	10.61 ± 13.94	5.90 ± 9.89	4.19 ± 4.79
Change (95% CI)	-1.68 (−6.53 to 3.16)	-2.13 (−8.84 to 4.59)	-1.07 (−6.46 to 3.71)	0.72 (−3.48 to 3.41)
p-value	0.104	0.552	0.225	0.410
OSDI				
FS-LASIK	16.71 ± 17.28	16.89 ± 14.77	14.37 ± 13.75	12.39 ± 10.78
SMILE	13.92 ± 12.32	20.35 ± 16.82	15.33 ± 14.74	13.20 ± 10.82
Change (95% CI)	2.79 (−4.79 to 10.38)	-3.46 (−11.58 to 4.66)	-0.96 (−8.83 to 5.97)	-0.81 (−9.52 to 3.35)
p-value	0.792	0.353	0.745	0.716
TM				
FS-LASIK	0.26 ± 0.09	0.30 ± 0.08	0.26 ± 0.08	0.29 ± 0.09
SMILE	0.27 ± 0.07	0.29 ± 0.11	0.27 ± 0.06	0.27 ± 0.08
Change (95% CI)	-0.01 (−0.05 to 0.03)	0.01 (−0.05 to 0.05)	-0.01 (−0.05 to 0.03)	0.02 (−0.02 to 0.07)
p-value	0.735	0.665	0.420	0.442
NI-TBUT				
FS-LASIK	14.23 ± 3.10	14.09 ± 3.29	13.76 ± 2.99	14.13 ± 2.87
SMILE	14.61 ± 3.75	12.54 ± 4.27	14.17 ± 4.52	14.00 ± 3.65
Change (95% CI)	-0.38 (−2.13 to 1.39)	1.55 (−0.39 to 3.49)	-0.41 (−2.35 to 1.53)	0.13 (−1.21 to 2.27)
p-value	0.391	0.187	0.935	0.321
Redness				
FS-LASIK	0.88 ± 0.40	0.87 ± 0.25	0.84 ± 0.37	0.88 ± 0.34
SMILE	0.80 ± 0.42	0.90 ± 0.38	0.79 ± 0.34	0.83 ± 0.38
Change (95% CI)	0.08 (−0.13 to 0.30)	-0.03 (−0.20 to 0.13)	0.05 (−0.13 to 0.25)	0.05 (−0.11 to 0.28)
p-value	0.741	0.041 *	0.766	0.801
IM				
FS-LASIK	0.89 ± 0.63	0.86 ± 0.69	0.74 ± 0.70	0.89 ± 0.63
SMILE	0.96 ± 0.82	0.96 ± 0.77	1.00 ± 0.64	1.04 ± 0.69
Change (95% CI)	-0.07 (−0.45 to 0.30)	-0.10 (−0.48 to 0.27)	-0.26 (−0.61 to 0.10)	-0.15 (−0.49 to 0.19)
p-value	0.840	0.602	0.138	0.378

Dry eye questionnaires

Mean baseline VAS score for the study and control groups was 6.01 ± 10.04 and 7.10 ± 8.63 respectively (p = 0.461). Lower VAS scores were observed in the study group (3.67 ± 7.09) compared to the control group (6.98 ± 11.73) at third month postoperatively, although such difference did not reach statistical significance (change −3.31, 95% CI −8.50 to 1.38; p = 0.101). After 6 months, VAS scores were comparable between groups (Table 4 & Fig. 2).

For the OSDI questionnaire, mean score at baseline for study and control groups was 16.13 ± 15.77 and 14.90 ± 15.05 respectively (p = 0.750). During follow-up, the treatment group showed a tendency towards lower OSDI scores compared to the control group, becoming later equivalent by the end of the study (14.87 ± 10.17 vs 21.97 ± 19.30 at first month; 10.74 ± 9.28 vs 19.21 ± 17.00 at third month and 12.85 ± 9.45 vs 12.60 ± 12.09 at sixth month). A statistically significant difference was observed at the third post-operative month (change −8.47, 95% CI −15.68 to −1.80; p = 0.043) (Table 4 & Fig. 2). The effect size, Cohen's d, for the OSDI score at the third month was 1.29.

Tear film

Tear meniscus height at baseline showed non-significant differences (p = 0.386) in both groups (study 0.27 ± 0.07 vs control 0.26 ± 0.09), but throughout the follow-up period the study group obtained statistically significant higher scores (p < 0.05) in all visits (Table 4 & Fig. 2). The effect size, Cohen's D, for the TM at the first, third and sixth month were 0.55, 0.71 and 0.75 respectively.

In terms of NI-TBUT, no significant differences were observed at baseline (study; 14.34 ± 3.83 vs control; 14.44 ± 2.88; p = 0.632), but a trend towards higher values was also observed in the study group (14.33 ± 3.24 vs 12.50 ± 4.13 at first month; 14.48 ± 3.78 vs 13.35 ± 3.54 at third month and 14.92 ± 3.11 vs 13.24 ± 3.09 at sixth month), with statistically significant difference at the sixth month (change 1.68 s, 95% CI 0.30–3.59; p = 0.039) (Table 4 & Fig. 2). Cohen's D, for the NI-TBUT at the sixth month was 0.54.

Ocular redness

Regarding conjunctival hyperemia, no differences were observed between groups (p > 0.05) at any point of the follow-up, indicating that IPL therapy did not result in a higher degree of surface redness (Table 4 & Fig. 2).

Upper and lower meibomian glands

Infrared meibography (IM; analyzed according to the degree of loss using the Jenvis grading scale) mean at baseline was 0.94 ± 0.77 vs 0.90 ± 0.66 for the study and control groups respectively (p = 0.968). IM showed a significant improvement (p < 0.05) in the treatment group vs control group throughout the entire study period (0.68 ± 0.65 vs 1.13 ± 0.73 at first month; 0.65 ± 0.71 vs 1.07 ± 0.59 at third month and 0.77 ± 0.63 vs 1.14 ± 0.64 at sixth month respectively) (Table 4 & Fig. 2). The effect size, for the IM at the first, third and sixth month were 0.65, 0.64 and 0.58 respectively.

A GEE analysis revealed low correlation between fellow eyes in TM, NI-TBUT, and IM. Therefore, the analysis was extended in these outcomes to include all eyes from the study sample, showing statistically significant results for these variables at all follow-up visits (Table 5).

Finally, when comparing pre- and post- treatment outcomes within each group (Table 6), we observed a statistically significant improvement in the OSDI score (change 5.39, 95% CI −0.22 to 10.29; p < 0.05), TM (change −0.02 mm, 95% CI −0.05 to 0.00; p = 0.045) and IM (change 0.29, 95% CI 0.05–0.53; p = 0.020) at the 3rd post-operative month in the study group only, while in the control group a significant worsening of the TM (change 0.02 mm, 95% CI 0.00–0.04;

Table 3
Statistical analysis of visual and aberrometric data in the study group compared to the placebo. UDVA: uncorrected distance visual acuity; CDVA; corrected distance visual acuity; SE: Spherical equivalent; PSF: point spread function; HOA: high order aberration.

	Study group Mean ± SD	Control group Mean ± SD	Change (95% CI)	p-value
UDVA				
Pre	0.13 ± 0.14	0.29 ± 0.35	-0.16 (−0.29 – - 0.02)	0.460
1 M	1.00 ± 0.18	0.97 ± 0.21	0.03 (−0.07 to 0.13)	0.418
3 M	1.04 ± 0.16	0.99 ± 0.22	0.05 (−0.06 to 0.14)	0.312
6 M	1.03 ± 0.19	1.01 ± 0.22	0.02 (−0.08 to 0.13)	0.568
CDVA				
Pre	1.09 ± 0.14	1.10 ± 0.12	-0.01 (−0.08 to −0.05)	0.702
1 M	1.08 ± 0.14	1.05 ± 0.14	0.03 (−0.04 to 0.10)	0.257
3 M	1.09 ± 0.14	1.09 ± 0.13	0.00 (−0.07 to 0.07)	0.762
6 M	1.10 ± 0.14	1.10 ± 0.13	0.00 (−0.06 to 0.08)	0.418
Sphere				
Pre	-2.25 ± 3.45	-1.85 ± 4.06	-0.40 (−2.13 to 1.53)	0.649
1 M	0.04 ± 0.54	-0.08 ± 0.46	0.12 (−0.13 to 0.38)	0.916
3 M	0.15 ± 0.48	-0.05 ± 0.42	0.20 (−0.03 to 0.45)	0.133
6 M	0.16 ± 0.63	-0.07 ± 0.46	0.23 (−0.07 to 0.48)	0.153
Cylinder				
Pre	-0.98 ± 0.98	-1.21 ± 1.07	0.23 (−0.29 to 0.76)	0.236
1 M	-0.20 ± 0.23	-0.21 ± 0.29	0.01 (−0.13 to 0.15)	0.843
3 M	-0.21 ± 0.31	-0.29 ± 0.31	0.08 (−0.09 to 0.24)	0.319
6 M	-0.17 ± 0.28	-0.23 ± 0.33	0.06 (−0.09 to 0.23)	0.472
SE				
Pre	-2.73 ± 3.22	-2.45 ± 3.95	-0.28 (−2.13 to 1.53)	0.767
1 M	-0.06 ± 0.53	-0.19 ± 0.48	0.13 (−0.13 to 0.39)	0.777
3 M	0.05 ± 0.48	-0.19 ± 0.39	0.24 (0.01 – 0.47)	0.022 *
6 M	0.04 ± 0.55	-0.17 ± 0.41	0.21 (−0.02 to 0.48)	0.105
PSF				
Pre	0.25 ± 0.11	0.26 ± 0.12	-0.01 (−0.07 to 0.05)	0.740
1 M	0.23 ± 0.10	0.25 ± 0.09	-0.02 (−0.06 to 0.04)	0.702
3 M	0.27 ± 0.12	0.27 ± 0.12	0.00 (−0.07 to 0.06)	0.691
6 M	0.25 ± 0.11	0.24 ± 0.10	0.01 (−0.06 to 0.06)	0.941
Coma				
Pre	0.31 ± 0.18	0.28 ± 0.15	0.03 (−0.06 to 0.11)	0.874
1 M	0.38 ± 0.24	0.29 ± 0.15	0.09 (−0.01 to 0.20)	0.112
3 M	0.38 ± 0.23	0.36 ± 0.16	0.02 (−0.08 to 0.12)	0.867
6 M	0.39 ± 0.15	0.37 ± 0.17	0.02 (−0.7 to 0.10)	0.522
Coma-like				
Pre	0.36 ± 0.16	0.34 ± 0.16	0.02 (−0.07 to 0.10)	0.713
1 M	0.45 ± 0.21	0.36 ± 0.15	0.09 (0.00 – 0.19)	0.093
3 M	0.44 ± 0.22	0.43 ± 0.15	0.01 (−0.09 to 0.12)	0.981
6 M	0.48 ± 0.17	0.45 ± 0.16	0.03 (−0.07 to 0.11)	0.424
Spherical				
Pre	0.29 ± 0.07	0.28 ± 0.08	0.01 (−0.03 to 0.05)	0.874
1 M	0.28 ± 0.15	0.25 ± 0.17	0.03 (−0.05 to 0.12)	0.263
3 M	0.26 ± 0.16	0.26 ± 0.21	0.00 (−0.10 to 0.10)	0.855
6 M	0.29 ± 0.15	0.24 ± 0.22	0.05 (−0.06 to 0.14)	0.549
Spherical-like				
Pre	0.31 ± 0.06	0.31 ± 0.08	0.00 (−0.03 to 0.05)	0.762
1 M	0.36 ± 0.09	0.32 ± 0.14	0.04 (−0.02 to 0.11)	0.151
3 M	0.34 ± 0.09	0.36 ± 0.12	-0.02 (−0.07 to 0.04)	0.981
6 M	0.36 ± 0.10	0.37 ± 0.14	-0.01 (−0.07 to 0.06)	0.924
Total HOA				
Pre	1.10 ± 0.73	1.15 ± 0.83	-0.05 (−0.45 to 0.35)	0.983
1 M	0.89 ± 0.34	0.77 ± 0.32	0.12 (−0.05 to 0.29)	0.306
3 M	0.90 ± 0.39	0.90 ± 0.31	0.00 (−0.20 to 0.18)	0.750
6 M	0.92 ± 0.33	0.90 ± 0.33	0.02 (−0.17 to 0.18)	0.392

p = 0.002) was observed at the 3rd month (Fig. 3). No differences were observed at 6 months.

Discussion

The postoperative patient satisfaction rate of refractive surgery result is around 98.5%. [28] Nowadays, a special interest is focused on the alteration of the ocular surface that occurs after laser refractive surgery, since these two concepts are closely related.

The mechanisms by which surface alterations and dry eye occur after laser refractive surgery are not entirely clear. An increase in the concentration of interleukin-6 has also been demonstrated after SMILE and LASIK surgery, which suggests that MGD is also a factor in causing postoperative DES.[7]

When comparing different refractive surgery procedures, a considerable amount of literature suggests that SMILE has a lower risk of post-surgical dry eye compared to FS-LASIK. Although it is true that flap techniques such as LASIK produce a greater ablation of stromal nerves and, consequently, a higher incidence of aqueous-deficient dry eye. There is also evidence in the literature showing that the recovery of corneal sensitivity at 6 months is comparable to the one observed after SMILE.[20] Actually, some studies have shown no significant differences between the two techniques on this regard: Demirok et al.[21] compared both procedures and found that dry eye parameters, including TBUT,

Table 4
Descriptive analysis as mean, median, interquartile range, minimum and maximum of ocular surface parameters and statistical analysis in the study group compared to the placebo. VAS: visual analogue scale; OSDI: Ocular surface disease index; TM: tear meniscus; NI-TBUT: non-invasive tear break-up-time; IM: infrared meibography.

	Study group Mean ± SD	Median (IQR)	Min - max	Control group Mean ± SD	Median (IQR)	Min - max	Change (CI 95%)	p-value
VAS								
Pre	6.01 ± 10.04	1.75 (0.00 – 7.50)	0.00 – 46.25	7.10 ± 8.63	3.75 (0.00 – 12.18)	0.00 – 27.50	-1.09 (−5.90 to 3.71)	0.461
1 M	8.30 ± 9.85	5.00 (0.00 – 12.50)	0.00 – 32.50	10.50 ± 15.54	5.62 (0.00 – 12.50)	0.00 – 62.50	-2.19 (−8.84 to 4.45)	0.774
3 M	3.67 ± 7.09	1.50 (0.00 – 3.75)	0.00 – 34.00	6.98 ± 11.73	3.75 (0.00 – 7.50)	0.00 – 47.50	-3.31 (−8.50 to 1.38)	0.101
6 M	5.01 ± 7.20	0.00 (0.00 – 10.00)	0.00 – 22.50	4.19 ± 6.52	2.50 (0.00 – 6.25)	0.00 – 30.00	0.82 (−3.44 to 3.81)	0.562
OSDI								
Pre	16.13 ± 15.77	15.00 (2.00 – 23.00)	0.00 – 67.00	14.90 ± 15.05	12.00 (2.00 – 23.00)	0.00 – 56.00	1.23 (−6.68 to 9.14)	0.750
1 M	14.87 ± 10.17	15.00 (6.00 – 21.00)	0.00 – 42.00	21.97 ± 19.30	15.00 (6.00 – 38.00)	0.00 – 75.00	-7.10 (−14.96 to 0.77)	0.291
3 M	10.74 ± 9.28	10.00 (4.00 – 19.00)	0.00 – 34.00	19.21 ± 17.00	19.00 (5.00 – 29.00)	0.00 – 63.00	-8.47 (−15.68 to −1.80)	0.043 *
6 M	12.85 ± 9.45	10.00 (4.00 – 19.00)	0.00 – 35.00	12.60 ± 12.09	10.00 (2.50 – 26.50)	0.00 – 44.00	0.25 (−8.10 to 4.66)	0.964
TM								
Pre	0.27 ± 0.07	0.27 (0.22 – 0.30)	0.15 – 0.43	0.26 ± 0.09	0.25 (0.18 – 0.29)	0.15 – 0.52	0.01 (−0.03 to 0.05)	0.386
1 M	0.32 ± 0.09	0.32 (0.25 – 0.39)	0.19 – 0.70	0.27 ± 0.09	0.24 (0.21 – 0.34)	0.11 – 0.46	0.05 (0.01 – 0.11)	0.014 *
3 M	0.29 ± 0.07	0.30 (0.25 – 0.33)	0.15 – 0.43	0.24 ± 0.07	0.23 (0.18 – 0.28)	0.15 – 0.44	0.05 (0.02 – 0.09)	0.004 *
6 M	0.32 ± 0.08	0.29 (0.26 – 0.36)	0.21 – 0.50	0.26 ± 0.08	0.25 (0.19 – 0.33)	0.13 – 0.44	0.06 (0.01 – 0.10)	0.018 *
NI-TBUT								
Pre	14.34 ± 3.83	14.70 (11.97 – 16.82)	7.74 – 23.71	14.44 ± 2.88	15.00 (13.76 – 15.84)	4.21 – 20.00	-0.10 (−1.84 to 1.65)	0.632
1 M	14.33 ± 3.24	15.00 (12.27 – 17.00)	5.99 – 19.31	12.50 ± 4.13	12.80 (10.39 – 15.00)	2.00 – 19.88	1.83 (−0.07 to 3.73)	0.058
3 M	14.48 ± 3.78	14.66 (11.04 – 16.44)	7.54 – 22.18	13.35 ± 3.54	13.86 (11.47 – 15.58)	4.44 – 21.22	1.13 (−0.77 to 3.02)	0.277
6 M	14.92 ± 3.11	15.36 (13.15 – 17.00)	9.29 – 21.03	13.24 ± 3.09	14.54 (10.33 – 15.72)	6.71 – 16.73	1.68 (0.30 – 3.59)	0.039 *
Redness								
Pre	0.92 ± 0.50	0.85 (0.50 – 1.25)	0.10 – 2.30	0.77 ± 0.27	0.80 (0.55 – 1.00)	0.20 – 1.25	0.15 (−0.05 to 0.36)	0.302
1 M	0.85 ± 0.36	0.80 (0.55 – 1.25)	0.20 – 1.60	0.92 ± 0.26	0.90 (0.79 – 1.11)	0.35 – 1.35	-0.07 (−0.23 to 0.09)	0.256
3 M	0.82 ± 0.36	0.80 (0.55 – 1.10)	0.20 – 1.50	0.82 ± 0.36	0.85 (0.47 – 1.05)	0.15 – 1.55	0.00 (−0.18 to 0.19)	0.935
6 M	0.87 ± 0.40	0.87 (0.59 – 1.09)	0.20 – 1.75	0.86 ± 0.32	0.90 (0.60 – 1.03)	0.25 – 1.80	0.01 (−0.14 to 0.24)	0.945
IM								
Pre	0.94 ± 0.77	1.00 (0.00 – 1.00)	0.00 – 3.00	0.90 ± 0.66	1.00 (0.00 – 1.00)	0.00 – 2.00	0.04 (−0.33 to 0.40)	0.968
1 M	0.68 ± 0.65	1.00 (0.00 – 1.00)	0.00 – 2.00	1.13 ± 0.73	1.00 (1.00 – 2.00)	0.00 – 2.00	-0.45 (−0.81 to −0.10)	0.015 *
3 M	0.65 ± 0.71	1.00 (0.00 – 1.00)	0.00 – 2.00	1.07 ± 0.59	1.00 (1.00 – 1.00)	0.00 – 2.00	-0.42 (−0.76 – - 0.09)	0.012 *
6 M	0.77 ± 0.63	1.00 (0.00 – 1.00)	0.00 – 2.00	1.14 ± 0.64	1.00 (1.00 – 2.00)	0.00 – 2.00	-0.37 (−0.69 to −0.04)	0.030 *

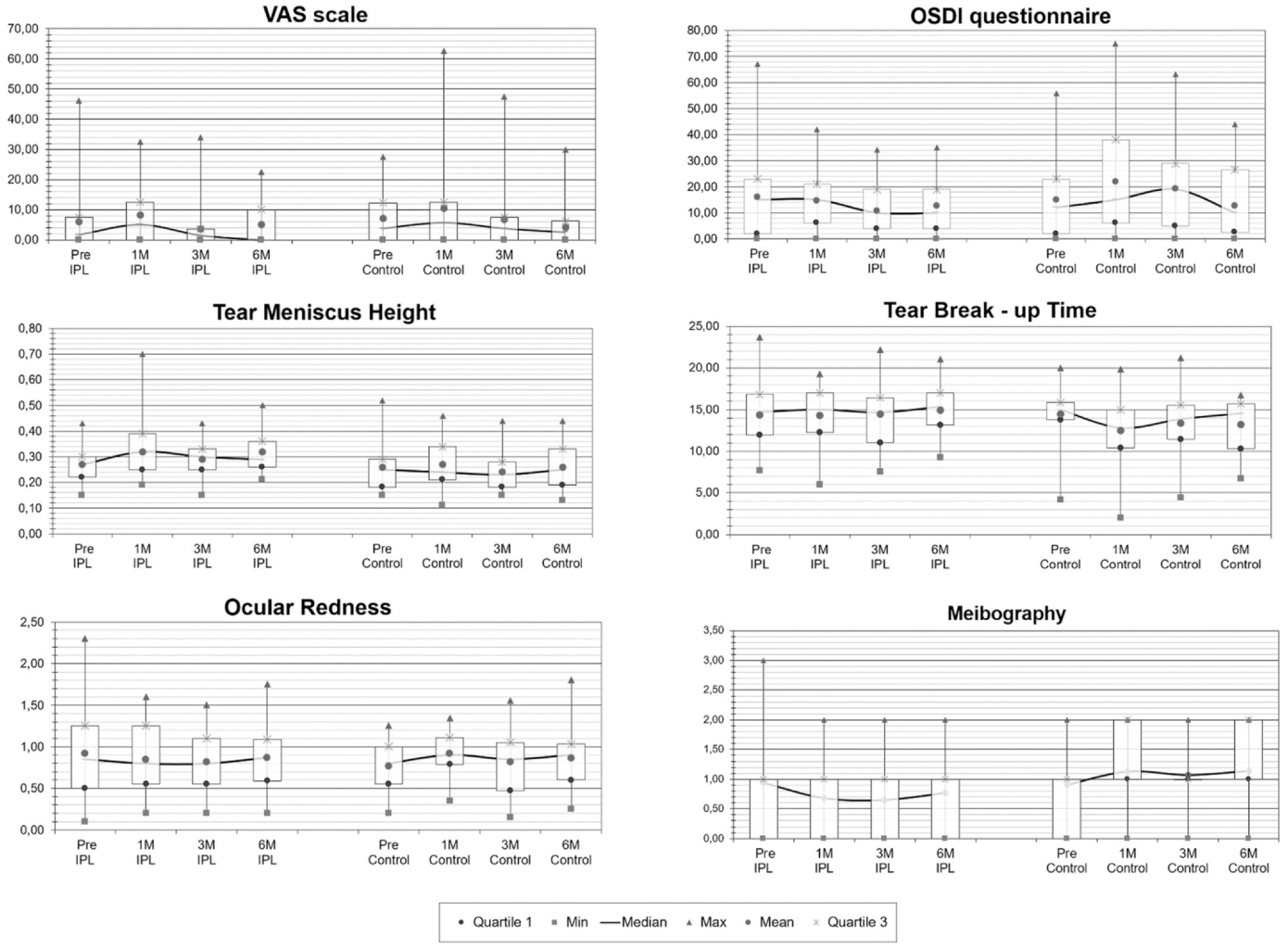

Fig. 2. Graphical representation of descriptive parameters (mean, median, minimum, maximum, first and third quartile) of ocular surface data.

Schirmer test and tear film osmolarity after surgery were not significantly different between both procedures at any time of the follow up. Li et al. [22] reported a marked and equivalent increase in OSDI scores after both surgical techniques. Xu et al.[23] discovered similar increases in subjective dry eye symptoms measured by the McMonnies questionnaire after both LASIK and SMILE. A meta-analysis published in 2016[24] reported results in terms of fluid quality and quantity after FS-LASIK and SMILE and showed no statistically significant changes in Schirmer's test, BUT and tear film osmolarity at 6 months at any point. Thus, they concluded that SMILE showed no clear competitive advantage in terms of ocular surface objective parameters compared to the FS-LASIK. A recent prospective randomized study of 88 eyes[25] compared ocular symptoms in patients undergoing FS-LASIK in one eye and SMILE in the contralateral eye, and no notable difference in self-

Table 5
Statistical analysis of the results obtained for variables with low correlation between eyes after GEE statistical analysis using data from both eyes (N = 122). TM: tear meniscus; NI-TBUT: non-invasive tear break-up-time; IM: infrared meibography.

	Treatment group Mean ± SD	Placebo group Mean ± SD	Change (CI 95%)	p-value
TM				
Pre	0.27 ± 0.07	0.27 ± 0.13	0.00 (−0.04 to 0.03)	0.285
1 M	0.32 ± 0.09	0.26 ± 0.10	0.06 (0.03 – 0.10)	0.000 *
3 M	0.29 ± 0.07	0.24 ± 0.08	0.05 (−0.03 to 0.08)	0.000 *
6 M	0.30 ± 0.07	0.26 ± 0.08	0.04 (0.02 – 0.07)	0.002 *
NI -TBUT				
Pre	13.95 ± 4.07	14.04 ± 3.01	-0.09 (−1.38 to 1.19)	0.754
1 M	14.44 ± 3.48	12.03 ± 4.12	2.41 (1.04 – 3.79)	0.001 *
3 M	14.71 ± 3.53	13.03 ± 3.31	1.68 (0.41 – 2.93)	0.007 *
6 M	15.03 ± 3.32	12.51 ± 3.25	2.52 (1.31 – 3.73)	0.000 *
IM				
Pre	0.95 ± 0.71	0.95 ± 0.72	0.00 (−0.26 to 0.26)	0.982
1 M	0.77 ± 0.64	1.10 ± 0.71	-0.33 (−0.57 to −0.09)	0.010 *
3 M	0.66 ± 0.65	1.13 ± 0.69	-0.47 (−0.72 to −0.22)	0.000 *
6 M	0.73 ± 0.61	1.14 ± 0.63	-0.41 (−0.64 to −0.18)	0.001 *

Table 6
Comparison of data before and after 3 and 6 months of IPL therapy using Wilcoxon signed-rank test. VAS: visual analogue scale; OSDI: Ocular surface disease index; TM: tear meniscus; NI-TBUT: non-invasive tear break-up-time; IM: infrared meibography.

	Change pre vs 3 M (CI 95%)	p-value	Change pre vs 6 M (CI 95%)	p-value
VAS				
Study group	2.34 (−0.58 to 5.25)	0.106	1.00 (−3.04 to 4.91)	0.529
Control group	0.12 (−4.96 to 4.76)	0.891	2.91 (−1.07 to 5.54)	0.135
OSDI				
Study group	5.39 (−0.22 to 10.29)	0.050 *	3.28 (−2.02 to 8.34)	0.367
Control group	- 4.31 (−11.17 to 3.04)	0.296	2.30 (−7.27 to 7.72)	0.474
TM				
Study group	-0.02 (−0.05 to 0.00)	0.045 *	-0.05 (−0.07 to −0.02)	0.112
Control group	0.02 (0.00 – 0.04)	0.002 *	0.00 (−0.02 to 0.03)	0.571
NI -TBUT				
Study group	-0.14 (−1.88 to 1.61)	0.799	0.58 (−2.27 to 1.27)	0.368
Control group	1.09 (−0.50 to 2.69)	0.086	1.20 (0.32 – 2.64)	0.061
Redness				
Study group	0.10 (−0.04 to 0.24)	0.386	0.05 (−0.11 to 0.15)	0.965
Control group	-0.05 (−0.15 to 0.01)	0.091	-0.09 (−0.16 to 0.01)	0.206
IM				
Study group	0.29 (0.05 – 0.53)	0.020 *	0.17 (−0.03 to 0.43)	0.083
Control group	-0.17 (−0.40 to 0.06)	0.132	-0.24 (−0.47 to 0.00)	0.052

reported dry eye symptoms was observed between the two study groups. The authors observed similar OSDI scores at any time point of the postop with no relationship between corneal denervation and subjective dry eye symptoms. These results are consistent with those from Damgaard et al.,[26] who also observed no significant differences in patient-reported dry eye symptoms at the 1- and 3-month follow-up visits between both techniques. Finally, Zhao et al.[27] recently published an evaluation of dry eye inflammation after SMILE and FS-LASIK and found that there were no notable differences between the groups in terms of tear meniscus, BUT, fluorescein corneal staining and Schirmer scores during each follow-up period. According to all these evidences, there is still controversy on whether SMILE is an better option than FS-LASIK regarding the postoperative risk of ocular surface disease. Although theoretical models have suggested that SMILE may result in less corneal nerve damage, this has not yet been clinically translated into a significant reduction in objective and subjective ocular surface parameters in real-clinical practice. For this reason, we decided to evaluate cases that underwent either FS-LASIK or SMILE (regardless the lamellar laser corneal refractive surgery technique used) where the study and control groups were divided only according to the use or not of perioperative IPL.

Few studies have already been conducted to test IPL therapy in patients who have undergone laser corneal surgery. Pazo et al.[12] were the first to analyze the technique, applying IPL to a group of 42 patients who had been diagnosed with post-LASIK refractory dry eye despite conventional treatment for at least 1 year and who underwent surgery in the previous 10 years. They obtained statistically significant results at 14 days in the NI-TBUT and at 28 days in the NI-TBUT, OSDI, tear film lipid layer and meibomian gland quality. However, their study presented several limitations: they only performed two IPL sessions, follow-up was limited to only one month, patient sample size was small, and they included information from both eyes in their statistical analysis. Additionally, control group was not masked or randomized. The same research group[13] recently published the results obtained from a prospective analysis of 50 patients with a previous diagnosis of moderate to severe post-LASIK dry eye for at least 1 year and who underwent surgery in the previous 10 years. Patients were randomized into two groups, one of which received two IPL sessions separated by two weeks, while the other group received two IPL sessions plus treatment with a heated eye mask, with a total follow-up of 28 days. Improvement in all dry eye parameters analysis was observed in both groups compared to baseline, with more pronounced results in the group treated with IPL and the heated eye mask. Comparing the results of these two studies[12,13] with the present study, we found that both studies showed improvement in objective NI-TBUT and subjective OSDI measures, even though our patients underwent surgery during the IPL treatment. However, it should be noted that in these previous studies the sample consisted in individuals with pre-existing post-laser dry eye and their target was its treatment, while our study was applied to healthy individuals having surgery as our goal was the prevention of the disease instead of its secondary treatment.

The effectiveness of perioperative IPL therapy has also been studied in cataract surgery. Ge et al.[14] conducted a prospective study with 60 randomized patients and obtained improvements in TBUT, OSDI, and meibomian gland function at 1 and 3 months postoperatively. The therapy was applied to a population with a previous diagnosis of mild to moderate MGD. These results are consistent with the ones presented in the current study.

To the best of our knowledge, this is the first study evaluating the use of IPL therapy as a perioperative technique to potentially prevent or

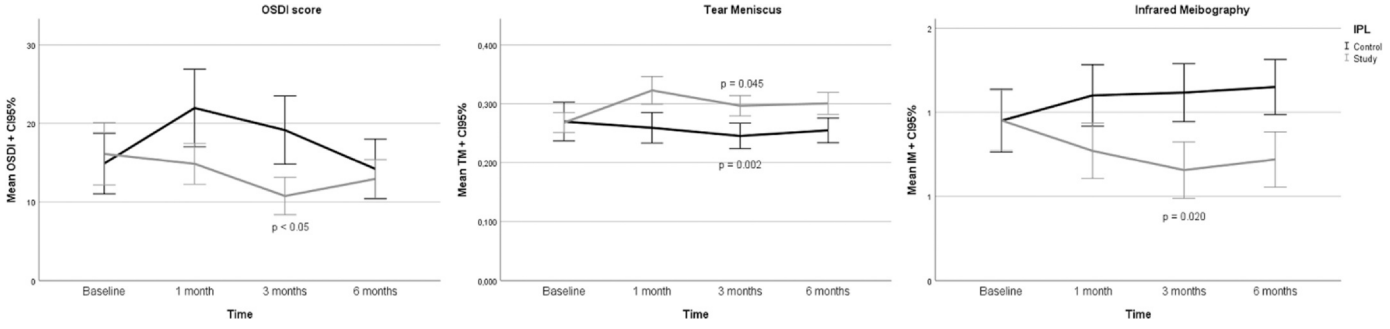

Fig. 3. Comparison pre- and post- treatment of results over time between both groups for OSDI, tear meniscus, and meibography.

improve the postoperative ocular surface disease after laser corneal refractive surgery. Our literature review also revealed a lack of randomized clinical trials to assess the effectiveness of IPL in this field. Our study is a randomized clinical trial in which healthy participants underwent three IPL sessions with a two-week interval between each session. IPL therapy proved to be safe for patients before and after refractive surgery, as no adverse effects were reported. Data regarding efficacy showed a significant improvement in the treatment group with moderate-high effect size in TM (change 0.05 mm, 95% CI 0.01–0.11; $p = 0.014$) and IM (change −0.45, 95% CI −0.81 to −0.10; $p = 0.015$) at first postoperative month, in OSDI score (change −8.47, 95% CI −15.68 to −1.80; $p = 0.043$), TM (change 0.05 mm, 95% CI 0.02–0.09; $p = 0.004$), and IM (change −0.42, 95% CI-0.76 to - 0.09; $p = 0.012$) at the third postoperative month, and in TM (change 0.06 mm, 95% CI 0.01–0.10; $p = 0.018$), NI-TBUT (change 1.68 s, 95% CI 0.30–3.59; $p = 0.039$), and IM (change −0.37, 95% CI −0.69 to −0.04; $p = 0.030$) at the sixth postoperative month. When performing an intra-group analysis at third month, a significant improvement in OSDI (change 5.39, 95% CI −0.22 to 10.29; $p < 0.05$), TM (change −0.02 mm, 95% CI −0.05 to 0.00; $p = 0.045$) and IM (change 0.29, 95% CI 0.05–0.53; $p = 0.020$) was observed for the IPL-treated group. In contrast, the control group showed a worsening of TM (change 0.02 mm, 95% CI 0.00–0.04; $p = 0.002$) compared to baseline. All these suggest that perioperative IPL seems to be beneficial for ocular surface in patients having laser corneal refractive surgery, since objective and subjective parameters improved in the IPL group compared to controls. On the other hand, OSDI differences faded after 6 months of observation, no significant benefit in patient's symptoms from IPL therapy was observed by the end of the follow-up. However, improvement in some of the objective parameters of ocular surface health such as the IM or the BUT remained.

Further studies shall examine if cost-effectiveness[29] justifies the use of IPL in every single patient receiving laser refractive surgery or, according to the evidence showed, focus on treating patients with higher risk preoperatively (pre-existing MGD and mild ocular surface disease).

The main limitation of the study was the lack of a larger sample size to allow a subgroup analysis according to the type of laser technique applied or the degree of preoperative refractive error. Moreover, due to the current low incidence of chronic post laser surgery dry eye syndrome[30], sufficient study sample needed to definitely establish the real role of IPL in the prevention of this threatening complication are difficult to be obtained by any clinical trial. Indeed, it is essential to highlight that our study sample was a Caucasian population residing in our Mediterranean area. Therefore, given the potential variations in MGD prevalence[31] and the diversity in skin types, there may be differences in responses to IPL therapy, which could vary depending on the population.

Conclusion

We present the first clinical trial investigating the role of perioperative IPL therapy as a prophylactic treatment in healthy individuals undergoing laser corneal refractive surgery. Our results suggest that perioperative IPL therapy applied in patients undergoing laser corneal refractive surgery improves objective ocular surface parameters postoperatively, including TM, NI-TBUT and IM. Additionally, it is suggested that IPL therapy could improve postoperative dry eye symptoms along the early postoperative period, as evaluated by the OSDI questionnaire.

Conflicts of interest disclosures

M. Amesty has received grants from L'Acuité (local distributor of Lumenis). The rest of authors have no financial or proprietary interests in any product or company associated with any device, instrument or drug mentioned in this article.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.apjo.2023.100029.

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