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Ocular Pain after Refractive Surgery

Interim Analysis of Frequency and Risk Factors

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Purpose: To examine the frequency and risk factors for ocular pain after laser assisted in situ keratomileusis (LASIK) and photorefractive keratectomy (PRK).

Design: Prospective study of individuals undergoing refractive surgery at 2 different centers.

Participants: One hundred nine individuals undergoing refractive surgery: 87% LASIK and 13% PRK.

Methods: Participants rated ocular pain on a numerical rating scale (NRS) of 0 to 10 before surgery and 1 day, 3 months, and 6 months after surgery. A clinical examination focused on ocular surface health was performed 3 and 6 months after surgery. Persistent ocular pain was defined as an NRS score of 3 or more at both 3 and 6 months after surgery (patients), and this group was compared with individuals with NRS scores of < 3 at both time points (control participants).

Main Outcome Measures: Individuals with persistent ocular pain after refractive surgery.

Results: The 109 patients who underwent refractive surgery were followed up for 6 months after surgery. Mean age was 34 $\pm$ 8 years (range, 23−57 years); 62% self-identified as female, 81% as White, and 33% as Hispanic. Eight patients (7%) reported ocular pain (NRS score $\geq$ 3) before surgery, with the frequency of ocular pain increasing after surgery to 23% (n = 25) at 3 months and 24% (n = 26) at 6 months. Twelve patients (11%) reported an NRS score of 3 or more at both time points and constituted the persistent pain group. Factors that predicted persistent pain after surgery in a multivariable analysis were (1) ocular pain before surgery predicated persistent pain after surgery (odds ratio [OR], 1.87; 95% confidence interval [CI], 1.06−3.31), (2) symptom report of depression before surgery (Patient Health Questionnaire-9: OR, 1.3; 95% CI, 1.1−1.6; $P = 0.01$), (3) use of an oral antiallergy medication before surgery (OR, 13.6; 95% CI, 2.1−89.3; $P = 0.007$), and (4) pain intensity day 1 after surgery (OR, 1.6; 95% CI, 1.2−2.2; $P = 0.005$). There were no significant associations between ocular surface signs of tear dysfunction and ocular pain, $P > 0.05$ for all ocular surface signs. Most individuals ($> 90\%$) were completely or somewhat satisfied with their vision at 3 and 6 months.

Conclusions: Eleven percent of individuals reported persistent ocular pain after refractive surgery, with several preoperative and perioperative factors predicting pain after surgery.

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Laser assisted in situ keratomileusis (LASIK) and photorefractive keratectomy (PRK) are commonly performed procedures used to correct refractive error. Although patient outcomes and satisfaction typically are excellent, a potential side effect is the occurrence of unpleasant eye sensations after surgery.[1] These sensations initially were labeled as "dry eye" (DE) because dryness was a commonly reported sensation. However, over time, these sensations were recharacterized as pain, given that other descriptors such as "burning," "aching," and "tenderness" also were used[2] and that patient symptoms often were discordant from DE signs, such as tear production and stability.[1] One prospective study examined symptoms before and after LASIK[3] using the Ocular Surface Disease Index (OSDI), a multifaceted questionnaire that captures information on pain, vision, symptom triggers, and visual function.[4] In active-duty Navy personnel, some individuals with low OSDI scores before surgery (OSDI score $\leq$ 12) showed higher scores after surgery (OSDI score $>$ 12: 27% [33 of 121]). However, many individuals reported an improvement in symptoms after surgery, with 59% (60 of 101) having an OSDI score of $>$ 12 before surgery that decreased to 12 or less after surgery.[3] A similar pattern was noted in a civilian population, with some individuals noting an increase and others a decrease in OSDI scores after refractive surgery.[3] Overall, the frequency of ocular symptoms after refractive surgery has been estimated to be 20% to 55% in studies that used different metrics to capture symptoms and had variable study designs and follow-up times (Table 1).[3,5−11] A limitation of the available studies is that

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ocular pain was not examined specifically, and thus, it is not possible to separate pain reports from the other eye symptoms that are captured in many standard clinical questionnaires, such as visual disturbances and tearing.

Many potential causes exist for the occurrence of ocular pain after refractive surgery, including nociceptive and neuropathic causes. Tear film abnormalities (e.g., tear instability, corneal epithelial disruption) have been noted after refractive surgery and are potential sources of nociceptive pain.[7] Corneal nerve damage also occurs at the time of refractive surgery, and studies have demonstrated that nerve density and sensitivity often do not return to baseline levels for years.[12] Maladaptive healing of nerves may contribute to the development of neuropathic pain in some individuals, as seen in other forms of persistent postoperative pain (PPOP).[1,13]

Despite recognition that ocular pain is a potential side effect of refractive surgery, no prospective studies have examined the frequency and risk factors for its development. Furthermore, retrospective studies that have examined chronic pain after refractive surgery have limitations with regard to pain definition and potential biases (e.g., recall, referral). One study identified 18 of 16 000 patients who reported severe ocular pain (not further defined) after LASIK, with a mean time to pain onset of 9.6 months.[14] Yet another study of 50 individuals with pain after refractive surgery (recruited from a corneal neuralgia Facebook group) found that pain started within 1 month of surgery in 46% of individuals.[15] To bridge knowledge gaps, we prospectively evaluated individuals before and after refractive surgery with a formal protocol to examine the frequency, quality, and risk factors for persistent ocular pain development.

Methods

Study Population

The institutional review boards of the University of Miami and Oregon Health & Science University approved this prospective study, the methods adhered to the tenets of the Declaration of Helsinki, and all patients signed an informed consent form before participation. Patients from both sites who elected to undergo refractive surgery in both eyes and who were receiving stable ocular and systemic medication for at least 3 months before surgery were eligible for inclusion in this study. Exclusion criteria included pregnancy; prior eye surgery; eye diseases that could confound ocular pain (glaucoma, herpetic eye disease); anatomic abnormalities of the eyelids, conjunctiva, or cornea; and age younger than 18 years. Of the 127 individuals enrolled in the study, 18 did not complete the 6-month visit and were considered lost to follow-up, leaving 109 patients included for analysis.

Data Collected

At the baseline visit before surgery, individuals filled out questionnaires that captured demographics, comorbidities (e.g., diabetes, hypertension, sleep apnea, migraine, thyroid problems, allergies [ocular and nonocular], and chronic pain conditions [e.g., fibromyalgia, temporomandibular joint disorder, trigeminal neuralgia, arthritis, and low back pain]), medications, and eye symptoms. In addition, a Schirmer test with anesthesia was performed. One day after surgery, individuals filled out questionnaires on eye symptoms since surgery. At the 3- and 6-month visits, individuals again filled out questionnaires and underwent a full ocular surface examination.

DE Symptoms

Two validated DE questionnaires, the 5-item Dry Eye Questionnaire (DEQ5)[16] and the OSDI,[4] were administered at baseline and at 3 and 6 months after surgery.

Ocular Pain

A numerical rating scale (NRS; range, 0−10) was used to assess pain intensity at all time points (before surgery and 1 day, 3 months, and 6 months after surgery). The NRS was chosen because it is a validated pain measure that has been used across multiple studies[17] and has been recommended as an outcome measure for clinical trials involving chronic pain by the International Association for the Study of Pain.[18] One day after surgery, individuals were asked to rate their worst eye pain intensity since surgery. At all other time points, individuals were asked to rate the intensity of their worst eye pain over the previous week. The Neuropathic Pain Symptom Inventory Modified for the Eye (NPSI-Eye)[19] was administrated before surgery and at 3 and 6 months after surgery. The Neuropathic Pain Symptom Inventory was developed to evaluate symptoms of neuropathic pain and subsequently was modified and validated for the evaluation of eye pain.[19] The NPSI-Eye interrogates eye pain characteristics over 5 dimensions (burning pain, paroxysmal pain, pressing pain, evoked pain, and paresthesia or dysesthesia), with individual scores (0−10) and a total score (0−100) generated.

Visual Acuity

Uncorrected and best-corrected visual acuity measurements were obtained at each visit.

Ocular Surface Examination

At the 3- and 6-month visits, ocular surface assessments included the following (in the order performed): (1) examination of the eyelid margin and grading of anterior blepharitis, eyelid vascularity (0 = none, 1 = mild, 2 = moderate, and 3 = severe), and inferior eyelid Meibomian orifice plugging (0 = none; 1 = less than one-third, 2 = between one-third and two-thirds, 3 = more than two-thirds of eyelid glands with visible plugs, graded without eyelid manipulation); (2) tear film breakup time (average of 3 measures in each eye); (3) corneal staining assessed using the National Eye Institute scale[20]; (4) pain assessment (0−10 on the NRS) before and 30 seconds after placement of topical anesthesia; and (5) the anesthetized Schirmer test.

Patient Satisfaction

At the 3- and 6-month follow-up visits, patients were asked to rate satisfaction with their vision on a 5-point scale. Answer options included completely satisfied, somewhat satisfied, neither, somewhat dissatisfied, and completely dissatisfied.

Assessed Comorbidities

At baseline, individuals filled out questionnaires regarding (1) demographics, (2) medications, (3) comorbidities, (4) nonocular pain via a pain history questionnaire, and (5) depression via the Patient Health Questionnaire-9 (PHQ9).[21] In addition, details of the surgical procedure were recorded, including treatment parameters and flap thickness.

Table 1. Summary of Some Prior Studies of Ocular Symptoms after Refractive Surgery

Study	No.	Procedure	Metric Used to Capture Symptoms	Population and Age (yrs)	Study Design	Outcome
Gong et al (2022)[5]	78	LASIK (n = 24), SMILE (n = 19), PRK (n = 35)	OSDI (high score = more severe symptoms)	Chinese; mean, 23.92 ± 4.65	P	OSDI scores ↑ 1 mo after surgery, returned to presurgical levels after 6 mos
Eydelman et al (2017)[3]	242	LASIK	OSDI ≤ 12 symptoms or > 12 symptoms	Navy personnel; mean, 29.1 ± 6.2	P	27% (33/121) without symptoms before surgery reported symptoms 3 mos after surgery; 19.5% (23/118) reported symptoms at 6 mos; 59% (60/101) with symptoms before surgery reported no symptoms 3 mos after surgery
Eydelman et al (2017)[3]	292	LASIK	OSDI ≤ 12 symptoms or > 12 symptoms	United States civilians; mean, 31.5 ± 7.3	P	27.5% (30/109) without symptoms before surgery reported symptoms 3 mos after surgery; 59% (87/147) with symptoms before surgery reported no symptoms 3 mos after surgery
Bower et al (2015)[6]	143	LASIK (n = 70), PRK (n = 73)	McMonnies Dry Eye Questionnaire	United States Army personnel; mean, 29.9 ± 5.2	P	McMonnies score ↑ 3, 6, and 12 mos after surgery compared with before surgery
Shoja et al (2007)[7]	190	LASIK	DE as defined by symptoms (soreness, scratchiness, dryness, grittiness, burning) plus TBUT < 10 plus corneal staining > 3/5 plus Schirmer test results < 10 mm	Iranians; mean, 31 ± 8	R	20% (38/190) had DE ≥ 6 mos after LASIK
Tuisku et al (2007)[8]	30	LASIK (n = 20); control participants (n = 10)	OSDI	Mean, 35.9 ± 8.8	R	OSDI higher 44.2 ± 11.3 mos after surgery vs. control participants (18.6 ± 13.4 vs. 7.5 ± 5.7)
Donnenfeld et al (2003)[9]	52	LASIK	Subjective rating (less dry, more dry, same as before LASIK)	Mean, 40.1	P	31% (16/52) reported eyes felt drier at 6 months vs. before LASIK
Albietz et al (2002)[10]	88	LASIK	Any symptom (sore, scratchy, dry, gritty, burning) sometimes, often, or constantly	Mean, 49 ± 9	R	14% (12/88) with symptoms before surgery; 32% (22/88) with symptoms ≥ 6 mos after surgery
Hovanesian et al (2001)[11]	828	LASIK (n = 587); PRK (n = 241)	Eye dryness rated as yes or no, sharp pains rated as yes or no	No demographic data	R	41% (99/241) PRK and 45% (266/587) LASIK reported dryness, 20% (49/241) PRK and 8% (48/587) LASIK reported sharp pain ≥ 6 mos after surgery

DE = dry eye; LASIK = laser assisted in situ keratomileusis; OSDI = Ocular Surface Disease Index; P = prospective; PRK = photorefractive keratectomy; R = retrospective; SMILE = small incision lenticule extraction; TBUT = tear film breakup time.

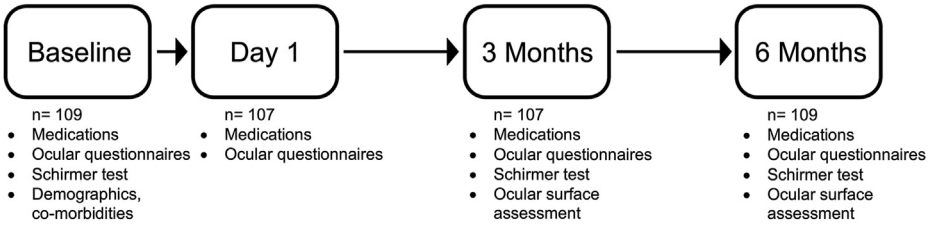

Figure 1. Diagram showing study time points and assessments.

Main Outcome Measure

Individuals with persistent ocular pain after refractive surgery, defined as an NRS score of 3 or more (rated at its worst intensity over the previous week) at both the 3- and 6-month time points, were included in the case group. This cutoff value was chosen based on prior work that defined an NRS score of 3 as moderate pain.[22]

Statistical Analysis

This is an interim analysis of a dataset generated from an ongoing study whose main aim is to identify diagnostic and prognostic tear biomarkers of persistent pain after refractive surgery. In this analysis, we studied the data generated from about the first half of the target sample of approximately 200 individuals. All statistical analyses were performed using SPSS software version 26.0 (SPSS, Inc). Descriptive statistics were used to summarize baseline and outcome variables. Paired methodologies (*t* test and McNemar test, as appropriate) were used to evaluate change over time within an individual. Tests for independent samples (*t* test and chi-square or Fisher exact tests, as appropriate) were used to examine differences between the 2 main groups, the case group, which comprised individuals with persistent ocular pain after surgery, and the control group, which comprised individuals without persistent pain defined as an NRS score of < 3 at both the 3- and 6-month time points. Multivariable logistic and linear regression analyses were performed to examine factors associated with pain after surgery after an inspection of residuals. Receiver operating characteristic curves were built based on factors that significantly predicted persistent pain on univariable analyses. Given the preliminary nature of the study, we opted to report all examined variables, with accompanying confidence intervals (CIs), and did not adjust *P* values for multiple comparisons, given potential limitations with this approach.[23]

Results

Study Population

One hundred nine individuals (51 at the Miami site and 58 at the Oregon Health & Science University site) were enrolled in the study between April 2021 and March 2022 and were followed up for 6 months after surgery (Fig 1). The mean age of the population was 34 ± 8 years (range, 23−57 years), and 62% self-identified as female, 81% as White, and 33% as Hispanic. The cohort overall was healthy, with 6 patients reporting hypertension, 5 patients reporting sleep apnea, 5 patients reporting arthritis (osteoarthritis, n = 3; rheumatoid arthritis, n = 2), and 4 patients reporting thyroid disease (not further subtyped). Twenty-three percent (n = 25) of individuals reported mild or worse depression symptoms (PHQ9 score ≥ 5) before surgery, with most symptoms falling in the mild range (PHQ9 score, 5−9; n = 20). Most individuals wore contact lenses before surgery (68% [n = 74]), and 17% (n = 18) reported a history of eye allergies. All individuals underwent bilateral eye surgery, with LASIK (87% [n = 95]) being more common than PRK (13% [n = 14]).

Frequency of Ocular Pain and DE Symptoms before Refractive Surgery

Before surgery, 8 patients (7% [n = 8]) rated their worst ocular pain as 3 or more on the NRS. Two individuals (2%) had a DEQ5 score of 12 or more before surgery, representing severe symptoms on a DE-specific questionnaire. When examined across all individuals, ocular pain scores (NRS) correlated with DE symptom scores (DEQ5: $r = 0.38$, $P < 0.001$; OSDI: $r = 0.26$, $P = 0.006$), highlighting the overlap in symptoms between pain-specific and DE questionnaires.

Frequency of Ocular Pain after Refractive Surgery

One day after surgery, most individuals (72% [n = 84]; 2 patients with missing responses) rated their worst postoperative pain as 3 or more on a 10-point NRS. No significant difference was found in acute pain at 1 day after surgery when assessed by surgery type (LASIK: 5.8 ± 3.1; PRK, 4.5 ± 3.0; $P = 0.14$). The frequency of ocular pain (NRS score ≥ 3) at 3 months (23% [n = 25]; 2 patients with missing responses) and 6 months (24% [n = 26]) after surgery was higher than before surgery. Overall, pain scores were worse at 3 and 6 months than at baseline ($P = 0.001$ for both) but were not significantly different between the 3- and 6-month time points ($P = 0.90$; Fig 2).

Twelve patients (11.0%; 11 receiving LASIK, 1 receiving PRK) reported an NRS score of 3 or more at both the 3- and 6-month time points and were defined as having persistent pain after refractive surgery (case group). Sixty-eight patients (64%) reported an NRS score of < 3 at both 3 and 6 months and were defined as having no persistent pain (control group). Twenty-seven patients (25%) had an NRS score of 3 or more at 1 time point after surgery but not both (n = 13 at 3 months; n = 14 at 6 months). When examining the entire study cohort, heterogeneity was noted with regard to pain intensity over time, as noted in Figure 3. Some patients in all groups (persistent pain; no persistent pain; NRS score > 3 at 3 or 6 months after surgery but not both time points) reported pain (NRS score > 3) before surgery, at 1 day after surgery, or both. In addition, some patients in the case group reported higher pain levels at 3 months after surgery than at 6 months after surgery, whereas others reported higher pain levels at 6 months after surgery than at 3 months after surgery (Fig 3).

Artificial tear use increased after surgery, with 13% (n = 14) of individuals reporting use before surgery and 73% (n = 79) and 65% (n = 71) reporting use at 3 and 6 months after surgery, respectively. However, it is noteworthy that use of artificial tears often is recommended by surgeons during the postoperative period.

Characteristics of Ocular Pain after Surgery

Characteristics of pain were extracted by examining responses to individual questions within the various pain- and DE-specific questionnaires. As with the preoperative findings, NRS pain scores and symptom scores on DE questionnaires were correlated at both the 3- and 6-month time points (3 months: DEQ5, $r = 0.68$; OSDI, $r = 0.40$; $P < 0.001$ for both; 6 months: DEQ5, $r = 0.58$; OSDI, $r = 0.62$; $P < 0.001$ for both).

At 6 months, the most common pain descriptors (via OSDI and NPSI-Eye) in the 12 individuals with persistent pain after surgery were "soreness" (n = 7), "grittiness" (n = 6), "burning" (n = 3), and "pressure" (n = 2). Three individuals reported that their eye pain increased with exposure to light, and 5 patients reported increased pain with exposure to wind. Ten individuals (n = 10 of 12 [83%]) reported a complete resolution of pain after topical anesthesia placement, with 2 patients (n = 2 of 12 [17%]) reporting persistent pain in at least 1 eye after topical anesthesia.

Risk Factors for Persistent Ocular Pain after Refractive Surgery

Several baseline risk factors were identified when comparing the 12 individuals with an NRS score of 3 or more at both the 3- and 6-month time points (case group) and the 68 individuals with an NRS score of < 3 at both time points (control group). On univariable analysis, the factors that increased the risk for persistent ocular pain after surgery were (1) the presence of ocular pain before surgery, assessed with both pain and DE questionnaires, and (2) the rating of pain on day 1 after surgery (Table 2).

A multivariable forward stepwise logistic regression model was built to examine all factors with a P value of < 0.15[24] in Table 2 in combination. In this model, preoperative symptoms of depression (PHQ9: OR, 1.3; 95% CI, 1.1−1.6; $P = 0.01$), pain intensity the day after surgery (OR, 1.6; 95% CI, 1.2−2.2; $P = 0.005$), and use of an oral antiallergy medication before surgery (OR, 13.6; 95% CI, 2.1−89.3; $P = 0.007$) were predictive of persistent pain after surgery.

Next, the significant factors on univariable or multivariable analysis (PHQ9, DEQ5, NRS assessed before surgery and day 1 after surgery, and use of an oral antiallergy medication before surgery) were combined and examined in receiver operating characteristic curve analysis, with a resulting area under the receiver operating characteristic curve of 0.90 (standard error, 0.04; 95% CI, 0.83−0.97), suggesting that these factors had a reasonable ability to discriminate between those with and without persistent pain.

Risk Factors for Pain at 3 and 6 Months after Surgery

We next examined which factors remained predictive of pain at each separate time point (3 and 6 months) with forward stepwise linear regression analyses. In each model, we considered all captured preoperative variables, pain intensity 1 day after surgery, and ocular surface signs 3 or 6 months after surgery. Both analyses resulted in similar findings: pain symptoms (captured with pain- or DE-specific questionnaires) before surgery (3 months: DEQ5, standardized $\beta = 0.29$; $P = 0.002$; 6 months: NRS, standardized $\beta = 0.20$; $P = 0.04$) and pain 1 day after surgery (3 months: NRS, standardized $\beta = 0.25$; $P = 0.008$; 6 months: NRS, standardized $\beta = 0.21$; $P = 0.04$) were predictive of postoperative pain.

Visual Outcomes and Patient Satisfaction

Ninety-two percent of individuals studied for this interim analysis achieved uncorrected vision of 20/25 or better in both eyes at 3 months. Patient satisfaction was high, with 93% and 91% of the entire population indicating that they were completely or somewhat satisfied with their vision in both eyes at 3 and 6 months,

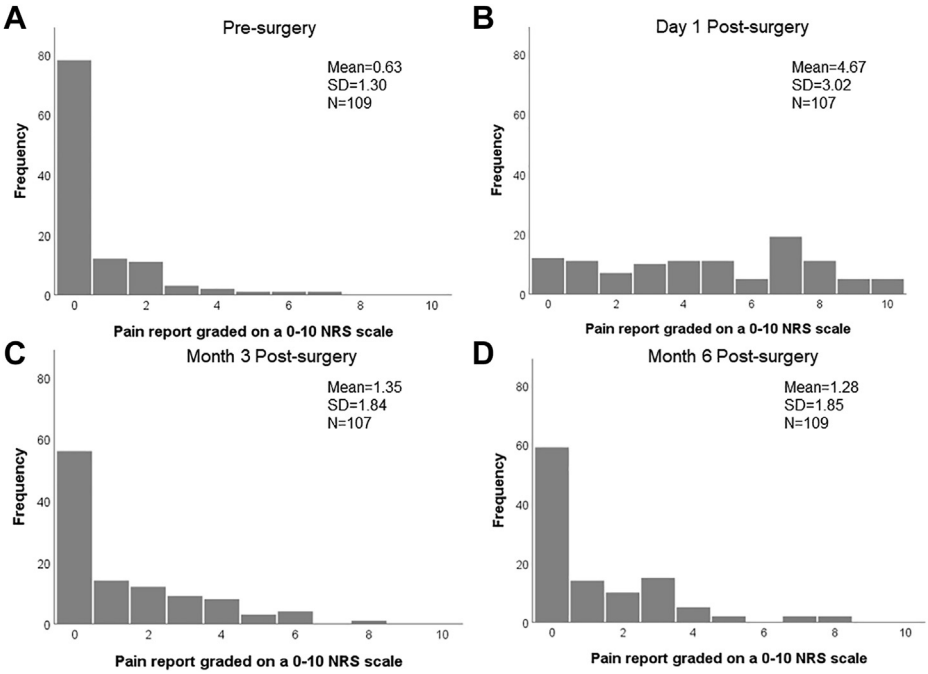

Figure 2. Bar graphs showing ocular pain score frequencies before and after surgery demonstrating an overall increase in pain scores at the 3- and 6-month visits compared with before surgery using a numerical rating scale (NRS): (**A**) before surgery, (**B**) day 1 after surgery, (**C**) month 3 after surgery, and (**D**) month 6 after surgery. SD = standard deviation.

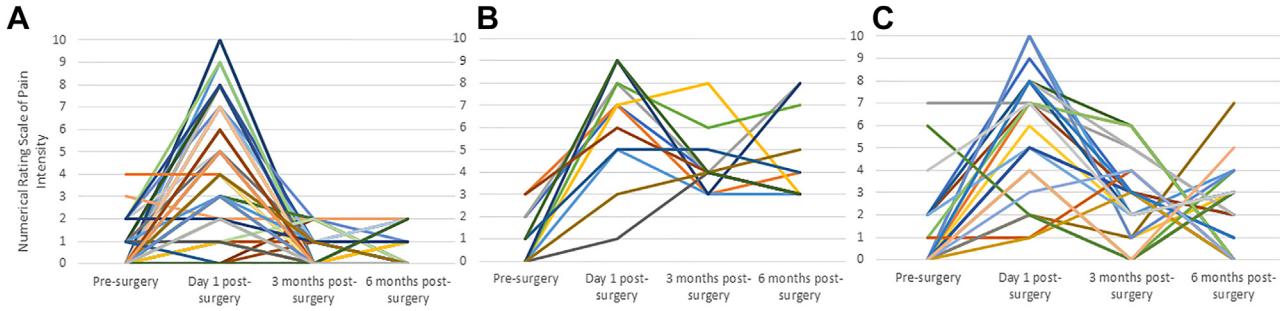

Figure 3. Line graphs showing individual pain intensity ratings demonstrating heterogeneity with regard to pain intensity before surgery and day 1 after surgery in all 3 groups: (**A**) 68 individuals without persistent pain (control group: NRS score < 3 at both 3 and 6 months), (**B**) 12 individuals with persistent pain (case group: NRS score ≥ 3 at 3 and 6 months), and (**C**) 27 individuals with pain at one, but not both, time points (3 or 6 months). Each individual line is shown in an arbitrary color to allow visual tracking of each individual over time. NRS = numerical rating scale.

respectively. The frequency of individuals satisfied or somewhat satisfied with the procedure was similar between those with versus without persistent pain.

Discussion

In this interim analysis, we found that 11% of individuals reported persistent ocular pain after refractive surgery, defined as pain intensity of 3 or more on a 0 to 10 scale at both 3 and 6 months after surgery. The pain was not related to visual acuity or ocular surface signs of disease (e.g., tear production, stability), suggesting that neuropathic mechanisms may contribute to this pain. Topical anesthesia eliminated pain in 10 of 12 individuals, further suggesting peripheral mechanisms at the 3- and 6-month times points in most individuals. Risk factors for persistent pain identified on univariable or multivariable analyses included (1) ocular pain before surgery, (2) symptoms of depression before surgery, (3) oral antiallergy medication use before surgery, and (4) ocular pain 1 day after surgery. Importantly, none of the patients demonstrated debilitating symptoms that necessitated an escalation of therapy beyond that typically used in the postoperative period (e.g., artificial tears).

Our findings are similar to reports of PPOP after non-ocular surgical procedures. Persistent postoperative pain generally is defined as pain that develops after surgery, that is at least 3 to 6 months in duration (after sufficient time has passed for the healing of tissues disrupted by surgery), and that is not explained by another cause of pain (e.g., infection). Persistent postoperative pain often has a neuropathic quality (burning, shooting, electriclike), and occurs spontaneously, in the absence of nociceptor activation.[25] The 11% estimate of PPOP in this study population is within the range reported for PPOP after other surgeries, including dental implants (8.5%−36%),[26] inguinal hernia repair (5%−30%),[27] thoracotomy (5%−65%),[27] and breast surgery (20%−50%).[27] Furthermore, some risk factors identified in our study for persistent ocular pain are shared with those from prior PPOP studies, including preexisting pain, acute pain, and depression.[28−38]

Regarding preexisting pain, pain 1 day before thoracotomy (assessed via an NRS of 0−10) increased the risk of postoperative pain 12 months after surgery (OR, 7.0; 95% CI, 2.4−20.2; n = 106).[32] With respect to acute pain, pain 1 hour after hysterectomy (assessed via an NRS of 0−10) increased the risk of postoperative pain 3 months after surgery ($r = 0.16$; $P < 0.05$; n = 200).[35] Regarding depression, preoperative depressive symptoms (assessed via the Hospital Anxiety and Depression Scale) increased the risk of postoperative pain 6 months after gastrointestinal surgery (NRS score ≥ 1 at rest: OR, 1.1; 95% CI, 1.01−1.2; $P = 0.03$; n = 274).[36] Our study adds pain and depressive symptoms before surgery and acute pain after surgery as risk factors for PPOP development after refractive surgery.

Specific to the eye, we previously reported that the presence of depression and ocular pain before surgery were risk factors for PPOP after LASIK. In a prospective study of 43 individuals undergoing LASIK, anxiety levels before surgery predicted ocular pain intensity scores (average NRS score over 1-week recall) 6 months after LASIK (anxiety symptom checklist-90: $\beta = 0.61$, $P < 0.0005$). In a similar manner, depression and ocular pain scores before surgery predicted neuropathic eye symptoms (via NPSI-Eye) 6 months after surgery (depression symptom checklist-90: $\beta = 0.50$, $P < 0.0005$; NRS: $\beta = 0.45$; $P < 0.0005$).[37] In the current study, we found that use of oral antiallergy medication before surgery was associated with PPOP after surgery. Interestingly, a similar finding was noted in a prior study in which oral antihistamine use predicted PPOP using a DE-specific questionnaire 6 months after cataract surgery (DEQ5 ≥ 6: OR, 6.2; 95% CI, 2.2−17.8: $P = 0.0003$; n = 119).[38] The mechanisms behind these associations are not clear and likely are multifactorial, including biological, psychological, and socioeconomic factors.[39] However, some hypotheses may be postulated. For example, inflammation in multiple compartments may impact both mental health and pain,[40] and the propensity for a proinflammatory state can have genetic and epigenetic origins.[41] Oral allergy medications, such as antihistamines, inhibit effects mediated by histamine. In the peripheral nervous system, this blockade can translate into activation and sensitization of nociceptive sensory nerve fibers.[42,43] Future studies are needed that examine mechanisms that may underlie our noted associations.

As with all studies, the study limitations need to be considered when interpreting our results. First, we defined

Table 2. Demographics, Comorbidities, and Ocular Surface Metrics of Patients with Persistent Postoperative Pain Compared with Control Participants without Persistent Pain

Variable	Persistent Pain (n = 12)	No Persistent Pain (n = 68)	P Value
Demographics			
Age (yrs)	33.3 ± 7.7	33.6 ± 7.6	0.90
Female sex	67% (8)	59% (40)	0.75
Race			0.07
White	58% (7)	78% (53)	
Black	0% (0)	6% (4)	
Asian	17% (2)	12% (8)	
Other	25% (3)	4% (3)	
Hispanic ethnicity	42% (5)	32% (22)	0.53
Current smoker	8% (1)	15% (10)	1.00
Location Miami	58% (7)	43% (30)	0.34
Comorbidities			
Hypertension	0% (0)	6% (4)	1.00
Sleep apnea using CPAP	0% (0)	6% (4)	1.00
Migraine or headache	17% (2)	16% (11)	1.00
Nonocular pain condition*	33% (4)	35% (24)	1.00
PHQ9 depression scale score	4.5 ± 4.9	2.4 ± 2.9	0.14
Depression (PHQ9 score ≥ 5)	33% (4)	21% (14)	0.45
Self-reported nonocular allergies	42% (5)	32% (22)	0.53
Oral medications			
Antidepressant	17% (2)	15% (10)	1.00
Anxiolytic	17% (2)	12% (8)	0.64
Antiallergy medication	33% (4)	10% (7)	0.06
Presurgical considerations			
DEQ5 score	4.9 ± 2.6	2.9 ± 2.9	0.03
OSDI score	8.3 ± 6.5	5.0 ± 7.4	0.16
NRS score			
Worst pain over past wk	1.0 ± 1.2	0.4 ± 0.8	0.01
Worst pain over past wk ≥ 3	17% (2)	3% (2)	0.11
NPSI-Eye	1.6 ± 2.8	0.8 ± 1.8	0.43
Schirmer test score (mm)†			
Mean at 5 min	16.5 ± 10.3	15.8 ± 10.3	0.92
< 5 at 5 min	17% (2)	12% (8)	0.64
Self-reported ocular allergies	33% (4)	13% (9)	0.10
Contact lens wear	75% (9)	75% (51)	1.00
Surgical considerations			
LASIK	92% (11)	90% (61)	1.00
Myopic ablation	100% (12)	97% (66)	1.00
Spherical equivalent more negative or positive value between eyes			
Myopic	−3.5 ± 1.3	−4.3 ± 1.7	0.11
Hyperopic	N/A	+2.8 ± 0.8	N/A
Flap depth for LASIK (μm)	119 ± 8.3	117 ± 9.0	0.52
NRS score			
Worst pain on postoperative day 1	6.3 ± 2.4	4.0 ± 3.0	0.02
≥ 3 on postoperative day 1	92% (11)	66% (45)	0.10
Ocular surface signs at 3 mos			
TBUT† (sec)	6.8 ± 1.9	8.0 ± 3.3	0.31
Corneal staining‡	1.6 ± 2.2	1.6 ± 2.2	0.95
Schirmer test score at 5 min (mm)†	15.2 ± 11.2	15.9 ± 10.8	0.84
Anterior blepharitis‡	0.3 ± 0.5	0.4 ± 0.7	0.66
Eyelid vascularity‡	0.9 ± 0.7	1.0 ± 0.9	0.73
Meibomian gland plugging‡	0.9 ± 0.3	0.8 ± 0.7	0.63
Ocular surface signs at 6 mos			
TBUT (sec)†	8.6 ± 3.7	8.1 ± 3.1	0.57
Corneal staining‡	0.9 ± 1.2	1.9 ± 2.6	0.22
Schirmer test score at 5 min (mm)†	15.7 ± 10.2	14.5 ± 9.9	0.71
Anterior blepharitis‡	0.6 ± 0.7	0.4 ± 0.7	0.38

Table 2. (Continued.)

Variable	Persistent Pain (n = 12)	No Persistent Pain (n = 68)	P Value
Eyelid vascularity‡	0.8 ± 0.6	0.9 ± 0.9	0.71
Meibomian gland plugging‡	1.0 ± 0.6	1.0 ± 0.6	0.48

CPAP = continuous positive airway pressure; DEQ5 = 5-item Dry Eye Questionnaire; LASIK = laser assisted in situ keratomileusis; N/A = not applicable; NPSI-Eye = Neuropathic Pain Symptoms Inventory Modified for the Eye; NRS = numerical rating scale; OSDI = Ocular Surface Disease Index; PHQ9 = Patient Health Questionnaire-9; TBUT = tear film breakup time.
Data are presented as percentage (number) or mean ± standard deviation, unless otherwise indicated. Persistent postoperative pain was defined as an NRS score of worst pain intensity over a 1-week recall of ≥ 3 at both 3 and 6 months after surgery. *P* values are indicated for univariable analyses of each factor.
*Includes a yes response to ever having any of the following conditions for >3 months: headache, arthritis, fibromyalgia, temporomandibular disorder, trigeminal neuralgia, low back pain, muscle pain, sciatica, shingles, postsurgical pain, tendonitis, chronic fatigue, irritable bowel syndrome, and interstitial cystitis.
†Higher value between the 2 eyes.
‡Lower value between the 2 eyes

persistent pain using specific questions at 2 time points (3 and 6 months) and thus cannot comment on pain evolution beyond the 6-month time point. Furthermore, we cannot comment on the location of pain within the eye (e.g., superficial, deep, eyelid). Second, our study recruited individuals undergoing refractive surgery in 2 geographical locations within the United States. Furthermore, because of limited space and capacity, not all individuals who met criteria for inclusion were offered enrollment in the study on a given day. As such, generalizability to geographically distinct populations and individuals not offered recruitment within our sites needs further examination. Third, we performed a comprehensive ocular surface examination at 3 and 6 months but did not include all potentially relevant tests, such as confocal microscopy and infrared meibography. Fourth, some measures we cannot tease out from our study, such as the motivation for artificial tear use after surgery (e.g., used because eyes felt uncomfortable or because ordered to use by the treating physician). Finally, unaccounted confounders (e.g., diet, environmental exposures) may have influenced our outcomes measures.

Despite these limitations, this study highlights that a minority of individuals experience persistent pain after refractive surgery and identifies risk factors for its development. Although these findings need to be validated in larger studies, this knowledge may inform preventive and treatment strategies that can be guided by literature on PPOP outside the eye. For example, with regard to prevention, in randomized clinical trials, oral neuromodulators (e.g., gabapentin, pregabalin) have been shown to decrease PPOP incidence after many, but not all, surgical procedures.[13] Dosing strategies have ranged from high-dose preoperative administration only to a low preoperative dose followed by an extended taper.[13] Although one small, randomized study using the latter approach (150 mg pregabalin twice daily started before refractive surgery and continued for 14 days) did not impact ocular pain symptoms after LASIK,[37] future studies in larger populations, perhaps in individuals at risk of PPOP development, are still warranted. Unique to the eye, neuromodulators also can be given in topical form, and some molecules have been found to improve corneal sensitivity and nerve growth after LASIK in animal models, including topical insulinlike growth factor-1,[44] macrophage migration inhibitory factor, and nerve growth factor.[45,46] Similar agents also have been studied as treatments for humans with presumed neuropathic ocular pain.[47,48] These lines of investigation are worthwhile because improvement in pain can translate into improved function and quality of life, preventing the development or lessening the morbidity of this condition. The future direction of the current study is to couple the clinical measures outlined above with tear proteins to develop prognostic and diagnostic models that can be used to identify individuals at high risk of pain development and to improve treatment approaches in individuals with pain, guided by the tear proteins of interest.

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Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. The Institutional Review Boards of the University of Miami and Oregon Health & Science University approved this prospective study. The methods adhered to the tenets of the Declaration of Helsinki. All patients signed an informed consent form prior to participation.

No animal subjects were included in this study.

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Data collection: Betz, Behrens, Harkness, Perez Blanco, Aicher, Galor

Obtained funding: N/A

Overall responsibility: Betz, Behrens, Harkness, Stutzman, Chamberlain, Perez Blanco, Hegarty, Aicher, Galor

Abbreviations and Acronyms:
CI = confidence interval; **DE** = dry eye; **DEQ5** = 5-item Dry Eye Questionnaire; **LASIK** = laser assisted in situ keratomileusis; **NPSI-Eye** = Neuropathic Pain Symptom Inventory Modified for the Eye; **NRS** = numerical rating scale; **OSDI** = Ocular Surface Disease Index; **PHQ9** = Patient Health Questionnaire-9; **PPOP** = persistent postoperative pain; **PRK** = photorefractive keratectomy.

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