

Prospective cohort study investigating frequency and risk factors for acute pain 1 day after refractive surgery

Jason Betz ,^{1,2} Elyana Vittoria Tessa Locatelli ,^{1,2} Brooke M Harkness,³ Maricarmen Perez-Blanco,¹ Steven J Everist,⁴ Siting Chen,⁵ Richard Stutzman,³ Winston Chamberlain,³ Afshan Nanji,³ Jodi Lapidus,⁵ Sue A Aicher,⁴ Anat Galor ^{1,2}

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¹Ophthalmology, University of Miami Health System Bascom Palmer Eye Institute, Miami, Florida, USA

²Ophthalmology, Bruce W Carter Department of Veterans Affairs Medical Center, Miami, Florida, USA

³Casey Eye Institute, Oregon Health & Science University, Portland, Oregon, USA

⁴Department of Chemical Physiology & Biochemistry, Oregon Health & Science University, Portland, Oregon, USA

⁵School of Public Health, Oregon Health & Science University, Portland, Oregon, USA

Correspondence to

Dr Anat Galor; AGalor@med.miami.edu

ABSTRACT

Background/aims To examine demographic and clinical factors associated with ocular pain 1 day after refractive surgery.

Methods Prospective study of individuals undergoing refractive surgery. Participants rated their ocular pain on a 0–10 numerical rating scale (NRS) presurgery and 1 day after surgery. Presurgery, participants completed questionnaires on demographics, comorbidities, medications and dry eye and ocular pain symptoms; and an anaesthetised Schirmer test was performed. Acute ocular pain 1 day after surgery was defined as an NRS score of worst pain since surgery ≥ 3 and this group was compared with individuals with NRS scores < 3 .

Results 251 individuals underwent refractive surgery (89% laser-assisted in situ keratomileusis, $n=222$; 11% PRK, $n=29$). Mean age was 35 ± 8 years (range 19 to 60); 60% ($n=150$) self-identified as female, 80% ($n=203$) as White, and 36% ($n=89$) as Hispanic. Thirteen (5%) individuals reported ocular pain (NRS ≥ 3) prior to surgery and 67% ($n=168$) reported ocular pain 1 day after surgery (nine individuals had pain at both time points). Factors that were associated with pain 1 day after surgery included Hispanic ethnicity (adjusted relative risk (aRR) 1.42, 95% CI 1.21 to 1.68, $p < 0.001$) and the presence of eye pain presurgery (aRR 1.10, 95% CI 1.02 to 1.18, $p=0.02$).

Conclusion A majority of individuals report moderate or greater pain within 24 hours of refractive surgery. Hispanic ethnicity and eye pain prior to surgery were associated with self-reported acute postsurgical pain.

INTRODUCTION

Refractive surgeries, such as laser-assisted in situ keratomileusis (LASIK) and photorefractive keratectomy (PRK), are widely performed procedures that correct refractive errors.¹ While both surgeries have proven effective in achieving excellent visual outcomes, the occurrence of pain and discomfort after surgery remain a concern, both in the acute period and chronically.^{2,3} In LASIK, a hinged corneal epithelial flap is created to expose the corneal stroma, photoablation is performed to reshape the cornea under the flap, and

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Acute pain can occur after refractive surgery with more data available on pain characteristics after photorefractive keratectomy (PRK) compared with laser-assisted in situ keratomileusis (LASIK).
- ⇒ Acute pain after surgery is a risk factor for chronic pain development.

WHAT THIS STUDY ADDS

- ⇒ A high proportion of individuals report acute ocular pain after both LASIK and PRK.
- ⇒ Hispanic ethnicity and pain prior to surgery are risk factors for ocular pain 1 day after surgery.
- ⇒ Culturally sensitive, evidence-based approaches are needed to optimise outcomes after refractive surgery.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Understanding which patients may be at higher risk for pain after surgery allows clinicians to more accurately counsel patient expectations.
- ⇒ Understanding risk factors for acute pain can help guide management and treatment of chronic pain.

the flap is repositioned. In PRK, the corneal epithelium is removed centrally and photoablation is performed directly on the anterior stroma.⁴ The frequency of postoperative pain after PRK has been examined in prior studies. In one study that quantified pain on a numeric rating scale (NRS, 0–10 scale), ocular pain ≥ 2 was present in 97% ($n=71$) of individuals in the postoperative period (mean NRS of 6.3 ± 2.5). In fact, a high proportion of individuals (52%, $n=38$) reported a pain intensity higher than 7.⁵ Unfortunately, less data are available on the incidence of acute pain after LASIK.

Information on the incidence and factors associated with acute pain after refractive surgery (eg, PRK and LASIK) could improve targeting and choice of prophylactic and therapeutic algorithms. Oral non-steroidal

anti-inflammatory drugs (NSAIDs) and opioids, topical NSAIDs, topical anaesthetics, cold patches and bandage soft contact lenses have all been used to mitigate acute pain after PRK.⁶ In a prospective study of 157 individuals, peak pain scores within 5 days of PRK (rated on a 0–10 NRS) were significantly lower in individuals who received topical (0.4% ketorolac) compared with oral (naproxen 220 mg) NSAIDs every 12 hours for 72 hours after surgery (4.2 ± 2.19 vs 5.82 ± 1.94 , $p<0.0001$, respectively).⁷ Similar studies are lacking with respect to management of acute pain after LASIK.

It is important to understand which patients are at risk for acute pain after refractive surgery as the presence of acute postsurgical pain has been identified as a risk factor for chronic pain development in ocular surgeries. In a retrospective study of 119 individuals who underwent cataract surgery, recall of higher acute postoperative pain during the first week after surgery (NRS 0–10) was a risk factor for persistent postoperative pain (OR 1.30, 95% CI 1.06 to 1.60).⁸ Acute pain has similarly been identified as a risk factor for chronic pain after refractive surgery.⁹ In our prospective study of individuals who underwent refractive surgery ($n=109$), ocular pain before surgery (OR 1.9, 95% CI 1.1 to 3.3, NRS 0–10) and ocular pain 1 day after surgery (OR 1.6, 95% CI 1.2 to 2.2, $p=0.005$, NRS 0–10) increased the risk of persistent pain after surgery (defined as NRS ≥ 3 at both 3 and 6 months).⁹ As such, understanding and addressing acute pain after refractive surgery may improve management of patients and long-term outcomes.

More information is thus needed on the frequency and risk factors for acute pain development after refractive surgery. Several studies have examined this question after surgeries outside the eye. In a retrospective study of 1041 unilateral total knee arthroplasty procedures, female gender (OR 1.76, 95% CI 1.31 to 2.36, $p<0.001$) and higher body mass index (OR 1.06, 95% CI 1.02 to 1.09, $p<0.001$) predicted ‘major pain’ 1 day after surgery (NRS ≥ 5 , 0–10 scale).¹⁰ Similar factors were identified in a prospective study of 466 individuals undergoing cataract surgery, with female gender ($\beta=0.21$, $p<0.001$), younger age ($\beta=-0.13$, $p=0.005$) and higher education level ($\beta=0.14$, $p=0.003$) predicting pain report 1 day after surgery (0–10 scale).¹¹ Our current study investigates the incidence, severity and risk factors for acute pain following both PRK and LASIK.

METHODS

Study population

Individuals undergoing refractive surgery at Bascom Palmer Eye Institute (BPEI) or Casey Eye Institute. The Institutional Review Boards of the University of Miami and Oregon Health & Science University (OHSU) approved this prospective study, the methods adhered to the tenets of the Declaration of Helsinki, and all patients signed an informed consent form prior to participation. Inclusion criteria included subjects who elected to undergo refractive surgery in both eyes and who were on stable ocular

and systemic medication for at least 3 months prior to surgery. 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 <18 years. All individuals underwent standard screening procedures and were deemed appropriate candidates for refractive surgery. Of note, ocular pain was not an exclusion criterion as it is a frequent finding in the general population¹² and in individuals who are appropriate candidates for refractive surgery.¹³ All patients underwent all study procedures in English.

Data collected

All individuals filled out questionnaires on demographics, comorbidities and medications. In addition, individuals filled out questionnaires regarding:

Dry eye symptoms

Two validated questionnaires, the 5 Item Dry Eye Questionnaire¹⁴ and the Ocular Surface Disease Index¹⁵ were administered prior to surgery.

Ocular pain

Individuals rated the intensity of their worst eye pain over the week prior to surgery and the current level of their eye pain immediately preceding and 30s after topical anaesthetic placement prior to the procedure on the day of surgery. One day after surgery, individuals rated the intensity of their worst eye pain since surgery. All pain intensities were rated on a 0–10 NRS. The Neuropathic Pain Symptom Inventory Modified for the Eye (NPSI-Eye)¹⁶ was also administered prior to and 1 day after surgery. The NPSI was developed to evaluate symptoms of neuropathic pain and was subsequently modified for evaluation of eye pain.¹⁶ The NPSI-Eye interrogates eye pain characteristics over five dimensions (burning pain, paroxysmal pain, pressing pain, evoked pain and paraesthesia/dysesthesia), with individual scores (0–10) and a total score (0–100) generated.

Mental health

Prior to surgery, individuals filled out questionnaires regarding depression via the Patient Health Questionnaire 9 (PHQ-9).¹⁷

Other measures included

Visual acuity

Prior to surgery, uncorrected, best-corrected visual acuity and manifest refraction were obtained.

Ocular surface examination

Prior to surgery, an anaesthetised Schirmer test was performed. The wetted length on the strip after 5 min was recorded to the nearest millimetre.

Surgical history

Details of the surgical procedure were recorded including treatment parameters and flap thickness. All individuals

received standard of care treatment during and after surgery.

Postsurgical considerations

Postsurgical medication regimens differed between the two sites. At both sites, all individuals received topical antibiotics and corticosteroids for postsurgical use. In addition, bandage contact lenses were placed in all individuals who underwent PRK and in some individuals who underwent LASIK. At OHSU, 2–3 drops of a topical NSAID (bromfenac 0.07%, Sun Pharmaceutical, California) were additionally instilled after surgery in all patients. Individuals undergoing PRK received a prescription for oxycodone with acetaminophen (Percocet, Endo Pharmaceuticals, Ireland) at OHSU or for acetaminophen 300 mg/codeine 30 mg (Tylenol #3, Mallinckrodt, UK) at BPEI to be used as needed.

Main outcome measure

Ocular pain was examined both as a continuous variable (0–10) and as a dichotomised variable NRS ≥ 3 versus < 3 . We defined cases as individuals with an NRS ≥ 3 at its worst 1 day after surgery (representing moderate or greater ocular pain) and controls as individuals with an NRS < 3 one day after surgery. This cut-off value was chosen based on a prior study suggesting an NRS of 3 as moderate pain.¹⁸

Statistical analysis

All statistical analyses were performed using SPSS V.26.0. Descriptive statistics were used to summarise baseline and outcome variables. A paired methodology (t-test) was used to evaluate change over time within an individual. Tests for independent samples (t-test and χ^2 or Fisher exact, as appropriate) were used to examine differences between our two main groups (cases: individuals with acute ocular pain after surgery, defined as an NRS ≥ 3 ; controls: individuals without acute pain defined as an NRS < 3). Multivariable Poisson modelling with robust error variances and linear regression analyses were performed to examine factors associated with pain 1 day after surgery after inspection of residuals. In the multivariate Poisson model, adjusted relative risk (aRR) was reported for each independent variable of interest. We opted to report all examined variables, with accompanying CIs, and did not adjust p values for multiple comparisons, given potential limitations with this approach and the exploratory nature of the study.¹⁹

RESULTS

Study population

We examined 251 individuals who underwent refractive surgery (89% LASIK, n=222; 11% PRK, n=29) at one site each in Florida (FL) and Oregon (OR). The mean age was 35 ± 8 years (range 19 to 60), and 60% (n=150) self-identified as female, 80% (n=203) as white, and 36% (n=89) Hispanic. Of the 89 individuals reporting Hispanic ethnicity, 85% (n=76) identified as white and

Hispanic. 5% (n=13) of individuals reported ocular pain before surgery, based on an NRS ≥ 3 for intensity of their worst eye pain over the week prior to surgery.

Acute pain after surgery

The day after surgery, the majority (67%, n=168) of individuals reported moderate or greater ocular pain (NRS ≥ 3) at some point within 24 hours since surgery (figure 1). The most frequently reported pain score was NRS=7 (16%, n=39), but individual NRS scores ranged from 0 to 10. More individuals had an NRS ≥ 3 at the Florida versus Oregon site (64%, n=107 vs 36%, n=61, $p < 0.001$).

Risk factors for acute pain

Individuals with acute pain after surgery were slightly younger than those without pain (33.7 vs 36.3 years, $p = 0.02$; $r = -0.164$, $p = 0.009$, table 1) and more likely to be Hispanic (45%, n=75 vs 17%, n=14, $p < 0.001$). Interestingly, pain scores 1 day after surgery were similar between individuals who underwent LASIK versus PRK (4.4 ± 3.0 vs 5.0 ± 3.3 , $p = 0.35$). Within the LASIK group, higher flap depth correlated with more pain 1 day after surgery ($r = 0.37$, $p < 0.001$). Pain ratings before surgery (1 week recall) were related to pain report 1 day after surgery (0.5 ± 1.1 to 4.5 ± 3.0 , paired t-test, $p < 0.001$, NRS 0–10). However, when examining this relationship with correlational analysis, no significant association was noted ($r = 0.09$, $p = 0.16$).

Regarding comorbidities, individuals who underwent refractive surgery were generally healthy, with a low frequency of accompanying medical conditions such as hypertension and diabetes. The most common comorbidities were depression, allergies and migraine, with frequencies that were similarly distributed between our groups. Regarding medications, antidepressants (12%, n=31), anxiolytics (14%, n=35), antiallergy medications (11%, n=27) and ADHD medications (9%, n=23) were the most used medications before surgery, with similar frequencies between groups. No patients were on systemic neuromodulators for pain at the time of surgery (table 1).

Multivariable models

A multivariable Poisson modelling with robust error variances was performed to examine all factors that predicted acute postsurgical pain in combination. In this model, Hispanic ethnicity (aRR 1.42, 95% CI 1.21 to 1.68, $p < 0.001$) and preoperative pain rating immediately before anaesthesia (aRR 1.10, 95% CI 1.02 to 1.18, $p = 0.017$) were predictive of pain 1 day after surgery. In a subanalysis, these two risk factors remained significantly associated with acute pain when considering only the individuals who had LASIK (data not shown).

DISCUSSION

In this analysis, we found that 67% of individuals reported moderate or greater ocular pain (NRS ≥ 3) 1 day

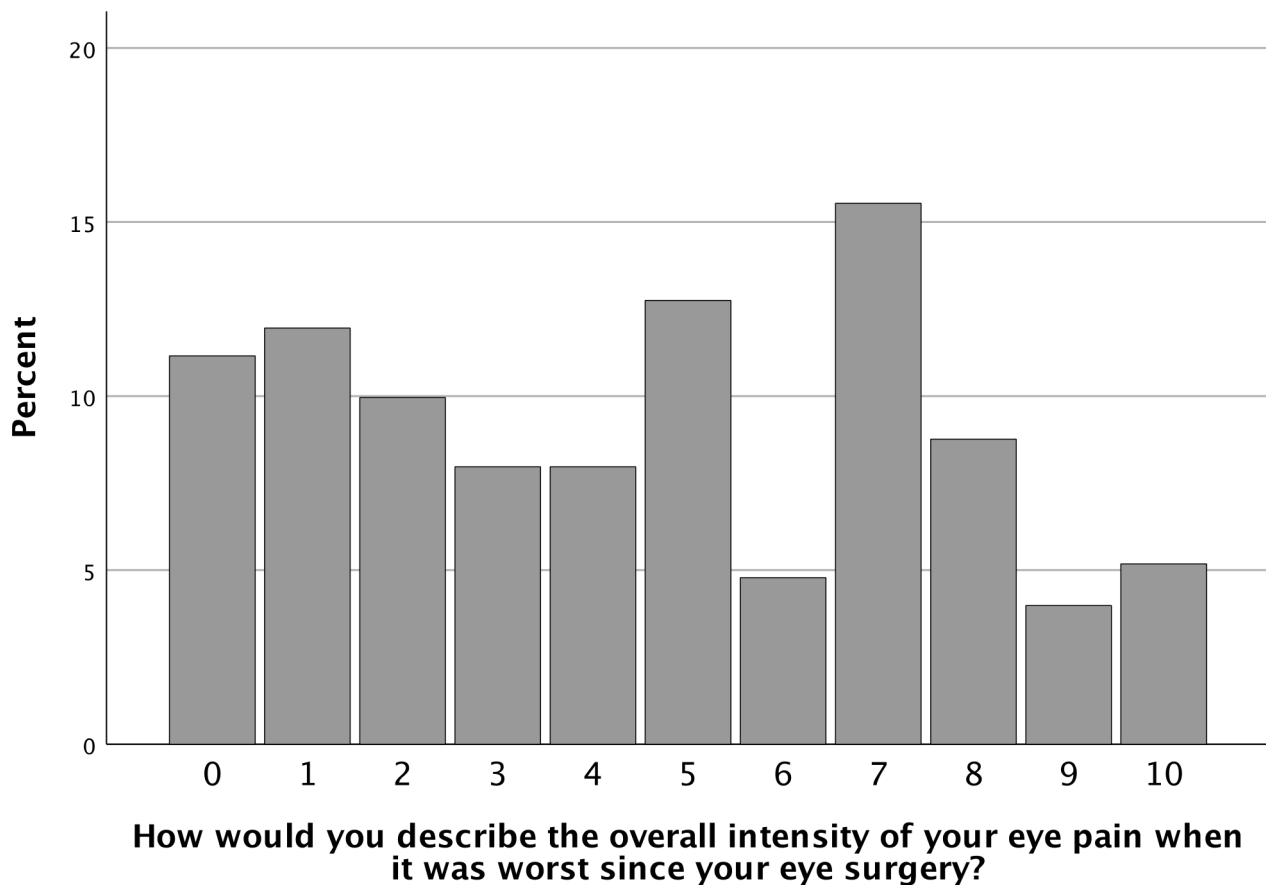


Figure 1 Histogram of ocular pain ratings 1 day after refractive surgery.

after refractive surgery. Surprisingly, pain report was not significantly different between individuals who underwent LASIK versus PRK. The frequency and intensity of acute ocular pain after refractive surgery are within the range of previous reports that examined acute pain after ocular surgery. For example, a Turkish study of 92 individuals found that 74% reported pain within 24 hours of cataract surgery (verbal pain scale >0, scale of 0–4).²⁰ A Chinese study of 110 individuals found that 49% reported pain 1 day after 20-gauge pars plana vitrectomy (NRS>0, scale of 0–10).²¹ These data suggest that a majority of individuals experience some degree of pain within 24 hours after ocular surgery.

In our study, acute pain report was related to some demographic factors, most notably ethnicity and age. Specifically, Hispanic individuals were more likely to report acute pain 1 day after surgery compared with non-Hispanics. Interestingly, prior studies have found relationships between Hispanic ethnicity, pain sensitivity and postsurgical pain.^{22–25} With respect to sensitivity, one prospective study of healthy adults (n=206) noted differences in pain tolerance by ethnicity. Specifically, Hispanic individuals were less tolerant of cold and heat (measured by hand immersion time in a cold bath, 53.6 vs 113.3s, p<0.05, and difference in temperature between heat detection and pain limit on the forearm, 4.7°C vs 6.0°C, p<0.05, respectively) compared with non-Hispanics.²⁴ With respect to postsurgical pain, a study of 114 veterans

found that Hispanic ethnicity increased the frequency of pain report 10 days after hand surgery (aRR 1.80, 95% CI 1.05 to 3.07, p=0.03, for average NRS ≥ 3).²⁵ While it is not clear why pain report was influenced by ethnicity in our study, pain sensitivity,²⁶ socioeconomic status²³ and cultural factors²⁷ have all been found to impact the pain experience. As such, culturally sensitive, evidence-based approaches to the diagnosis and treatment of acute pain, as well as additional research on pain perception, are needed to understand aspects of acute pain after refractive surgery.²⁸

Beyond ethnicity, we found that individuals with acute pain after refractive surgery were younger than their counterparts without pain. Similarly, younger age has been identified as a risk factor for acute pain after non-ocular surgeries.^{29–32} In a meta-analysis of 30 surgical procedures of 22 963 patients, older individuals were less likely to report pain after surgery compared with younger individuals (OR 0.79, 95% CI 0.76 to 0.82, for each 10 year age increase).²⁹ Age did not remain in our acute pain model, however, when other factors, such as ethnicity, were considered.

Several other variables, such as female gender,³³ presurgical anxiety³⁴ and depression,³⁵ have been identified as risk factors for acute postsurgical pain in prior studies but were not found to impact acute postrefractive surgery pain in our study. Pain prior to surgery, however, is a risk factor shared between prior work and our current study.

Table 1 Demographics, co-morbidities, medication use, eye symptoms and surgical information, grouped by the presence or absence of pain 1 day postsurgery (defined as NRS \geq 3 at its worst since surgery)

	No pain (NRS<3) (n=83)	Pain (NRS \geq 3) (n=168)	P value
Demographics and exposures			
Age, mean years \pm SD	36.3 \pm 7.9	33.7 \pm 8.0	0.02
Gender, % female (n)	60% (50)	60% (100)	0.91
Race, % White (n)	82% (68)	80% (135)	0.97
% Black (n)	2% (2)	4% (6)	
% Asian (n)	12% (10)	9% (15)	
% Other (n)	4% (3)	7% (12)	
Ethnicity, % Hispanic (n)	17% (14)	45% (75)	<0.001
Smoker, % current (n)	13% (11)	10% (17)	0.47
Smoker, % former (n)	24% (20)	23% (38)	0.81
Secondhand smoke exposure, % (n)	11% (9)	4% (7)	0.04
Systemic co-morbidities			
Diabetes, % (n)	2% (2)	1% (2)	0.60
Hypertension, % (n)	8% (7)	5% (9)	0.35
Sleep apnoea, % (n)	8% (7)	2% (4)	0.045
CPAP use, % (n)	5% (4)	2% (3)	0.22
Migraine or headache, % (n)	11% (9)	15% (25)	0.38
Rosacea, % (n)	5% (4)	4% (6)	0.73
Fibromyalgia, % (n)	4% (3)	0% (0)	0.04
Non-ocular pain condition, % (n)	16% (13)	10% (16)	0.15
Depression, PHQ-9, mean \pm SD	2.7 \pm 3.5	2.4 \pm 3.3	0.48
Depression (PHQ-9 \geq 5), % (n)	23% (19)	18% (30)	0.34
Non-ocular allergies, % (n)	43% (36)	35% (59)	0.21
Ocular co-morbidities			
Ocular allergies, % (n)	19% (16)	13% (21)	0.15
Contact lens wear, % (n)	75% (62)	74% (124)	0.88
Artificial tear use, % (n)	13% (11)	19% (31)	0.30
Oral medications			
Antidepressant, % (n)	13% (11)	12% (20)	0.76
Anxiolytic, % (n)	17% (14)	13% (21)	0.35
Anti-allergy medication, % (n)	16% (13)	8% (14)	0.08
ADHD medication, % (n)	12% (10)	8% (13)	0.27
Pre-surgery ocular symptoms			
DEQ5, mean \pm SD	3.3 \pm 3.0	3.5 \pm 3.2	0.59
OSDI, mean \pm SD	5.8 \pm 8.0	7.1 \pm 10.2	0.30
Worst pain over past week, mean \pm SD, range 0–10	0.4 \pm 1.0	0.5 \pm 1.1	0.54
Worst pain over past week \geq 3, % (n)	5% (4)	5% (9)	1.00
Pain immediately before anaesthesia, mean \pm SD, range 0–10	0.06 \pm 0.3	0.2 \pm 0.7	0.006
Pain 30s after anaesthesia, mean \pm SD, range 0–10	0.04 \pm 0.2	0.1 \pm 0.4	0.03
NPSI-Eye, mean \pm SD, range 0–100	0.9 \pm 1.6	1.0 \pm 2.5	0.58
Pre-surgery tear production			
Schirmer, mean mm at 5 min, mean \pm SD	16.7 \pm 10.4	17.2 \pm 11.1	0.71
Schirmer<5 mm at 5 min, % (n)	12% (10)	15% (25)	0.54
Pre-surgery refractive corrections			
Best corrected-visual acuity 20/20 or better, % (n)	84% (68)	87% (146)	0.53

Continued



Table 1 Continued

	No pain (NRS<3) (n=83)	Pain (NRS ≥3) (n=168)	P value
Manifest refraction spherical equivalent, mean±SD	-3.6±2.2	-3.4±2.1	0.39
Manifest refraction cylinder, mean±SD	0.71±0.63	0.81±0.80	0.30
Surgical considerations			
LASIK, % (n)	88% (73)	89% (149)	0.86
PRK, % (n)	12% (10)	11% (19)	0.86
Flap depth, mean µm±SD (range), LASIK only	113.7±7.05 (110-130)	120.6±8.96 (105-130)	<0.001
Surgical location, Miami, % (n)	27% (22)	64% (107)	<0.001
Hyperopic correction	4% (3)	3% (5)	0.72

CPAP, continuous positive airway pressure; DEQ5, 5 item Dry Eye Questionnaires; LASIK, laser assisted in situ keratomileusis; NPSI-Eye, Neuropathic Pain Symptoms Inventory-Modified for the Eye; NRS, numerical rating scale; OSDI, Ocular Surface Disease Index; PHQ-9, Patient Health Questionnaire.

In a prospective study of 228 adults who underwent ophthalmic surgery, preoperative pain based on NRS ≥ 5 predicted average acute postoperative pain at 1, 3, 6 and 24 hours after surgery (β -coefficient 0.263, $p < 0.001$).³⁶ These findings suggest that some factors, namely pain prior to surgery, may increase the risk of acute pain after surgery, irrespective of ocular surgery type.

Our current study further highlights that risk factors for acute and chronic pain after refractive surgery are not identical.⁹ While the presence of pain prior to surgery was a shared risk factor for acute and chronic pain, other factors were specific for acute or chronic pain.⁹ For example, symptoms of depression (PHQ-9 score) and use of oral antiallergy medication prior to surgery were risk factors for chronic but not acute pain; while Hispanic ethnicity was a risk factor for acute pain but not chronic pain development. These discrepancies support the need for further investigations into risk and protective factors that impact acute and chronic pain after ocular surgery.

As with all studies, it is important to consider the limitations of our study when interpreting the results. First, our study included individuals from two geographically different locations in the USA, with distinct patient populations. Therefore, our findings may not be generalisable to other US and global populations. Additionally, location-specific differences were noted in the frequency of acute postsurgical pain, a finding which needs further exploration and may be driven by the differential distribution of Hispanic individuals across sites. Second, comprehensive ocular surface examination data were not collected prior to surgery, so we were unable to investigate whether presurgical tear and anatomical parameters, such as tear stability and Meibomian gland features, relate to acute pain. However, tear production (Schirmer test) did not impact acute pain report. Third, patients undergoing refractive surgery are extensively counselled on the expectation of transient pain after surgery, which may impact perception and ratings of pain during the acute postoperative period. Fourth, differences in postsurgical pain management strategies between LASIK and PRK

and between the sites may have impacted pain reports, including the use of bandage contact lenses in all PRK patients but not all LASIK patients. Furthermore, while prescriptions were given for pain medications after PRK, it is not known which prescriptions were filled. Fifth, the low frequency of some comorbidities limits an interpretation of their contributions to postsurgical pain. Sixth, less individuals underwent PRK, which limited our ability to examine specific risk factors for acute pain in this population. Finally, self-reported diagnoses and unaccounted confounders (eg, diet, pain sensitivity, environmental factors) may have influenced our outcomes.

Despite these limitations, we found that a majority of individuals experienced moderate or greater pain 1 day after refractive surgery and we have identified several risk factors for acute pain presence. While our findings require validation in diverse populations, this line of research is important, since a better understanding of acute pain development may impact long-term outcomes. Multiple studies have identified acute pain as a predictor for chronic pain development^{8 9 37} and the prevention and mitigation of postsurgical pain have been shown to improve quality of life and decrease the psychological burden of pain on daily function.³⁸ Future studies are needed to clarify which interventions are most effectively in mitigating acute pain after refractive surgery.

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Contributors Conception and design: AG, SA. Analysis and interpretation: JB, EVTL, BMH, SC, RS, WC, AN, JL, SA, AG. Data collection: JB, EVTL, BMH, MP-B, SE, SA, AG. Overall responsibility: JB, EVTL, BMH, MP-B, SE, SC, RS, WC, AN, JL, SA, AG. Guarantor: AG

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Competing interests AG is an editor of BMJ Open Ophthalmology. There are no other competing interests.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Miami 20200807OHSU STUDY00020444 Methods: 'The Institutional Review Boards of the University of Miami and Oregon Health & Science University (OHSU) approved this prospective study, the methods adhered to the tenets of the Declaration of Helsinki, and all patients signed an informed consent form prior to participation'. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information.

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ORCID iDs

Jason Betz <http://orcid.org/0000-0003-2819-1374>

Elyana Vittoria Tessa Locatelli <http://orcid.org/0000-0001-7065-7196>

Anat Galor <http://orcid.org/0000-0002-3026-6155>

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