Predictors of Early Postoperative Pain After Photorefractive Keratectomy

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Purpose: To compare the profiles of postoperative photorefractive keratectomy (PRK) pain between both eyes under the same conditions and to verify the preoperative predictors of pain such as gender, anxiety, knowledge of the procedure, and spherical equivalent refractive error (SERE).

Methods: This prospective study included 86 eyes of 43 patients with myopia who underwent PRK in both eyes at an interval of 14 days between the procedures. Before surgery, subjects answered the State Anxiety Inventory. After surgery, usual PRK pain treatment was given. Subjects answered the Visual Analog Scale, the Brief Pain Inventory (BPI), and the McGill Pain Questionnaire at 1, 24, 48, 72, and 96 hours after surgery. Pain scores and anxiety were compared between each eye using the Wald test and paired Student *t* test, respectively. The Wald test was performed for gender and SERE for each eye separately.

Results: There were no statistically significant differences between both eyes for all time points regarding the Visual Analog Scale, BPI, and McGill Pain Questionnaire–Pain Rating Index pain scores. Subjects were less anxious on average before the second surgery compared with before the first surgery ($P < 0.001$); however, it was not related to pain ratings after surgery. Gender did not significantly affect any scale of pain, and the SERE between −3 diopters (D) and −5 D ($P = 0.035$) revealed effects on the BPI.

Conclusions: The profiles of postoperative pain after PRK were similar between both eyes under the same conditions. In this study, a high SERE was the only predictor for increased pain after PRK.

Key Words: photorefractive keratectomy, pain, predictors, postoperative

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Photorefractive keratectomy (PRK) is a refractive surgery performed with an excimer laser, which causes direct injury to the nerves of the treated corneal area including those of the epithelium and upper stromal layers.[1,2]

High temperatures and endogenous inflammatory mediators released by excimer laser energy and damaged corneal tissues or resident inflammatory cells stimulate nociceptors and produce pain. Postoperative exposure of the innervated stromal surface causes intense discomfort and acute postoperative pain even in patients using oral and ocular analgesics and nonsteroidal antiinflammatory drugs.[3,4]

Despite all research efforts to improve acute postoperative pain management,[5] patients undergoing PRK still exhibit unpredictably high pain scores that are comparable to fracture pain even 48 hours after surgery.[6]

There is a large amount of variation in pain among individuals with the same condition.[7] To provide effective individual analgesic treatment strategies, it would be desirable to preoperatively distinguish patients who are at high risk for developing severe postoperative pain from those who are at low risk. This strategy has been used successfully in various surgeries, including hip replacement arthroplasty, knee replacement arthroplasty, and spinal surgery.[8–10]

Important predictors of postoperative pain that have been reported outside of ophthalmology studies include gender, anxiety, and knowledge of the procedure.[11–13] High refractive errors require a larger quantity of laser treatment and deeper ablation. It is well known that the risk of haze is high for treatments using excimer lasers for high refractive errors.[14,15] However, the relationship between ablation and pain has not yet been shown to be a predictor of postoperative pain.

The first aim of this study is to evaluate whether there are differences in the profiles of postoperative pain after PRK between both eyes under the same conditions. The second aim is to verify the applicable preoperative predictors for the occurrence of early severe postoperative pain in patients undergoing PRK while controlling for potentially confounding variables.

MATERIALS AND METHODS

This study included 43 pairs of eyes of 43 patients who had a spherical equivalent refractive error (SERE) of less than −5 diopters (D) and a cylindrical component of the refraction less than −1 D. The exclusion criteria were absence of depression, other chronic diseases with overlapping pain conditions such as fibromyalgia, diabetes mellitus, and any continuous oral or topical medication. Patients who had taken any analgesic medication 24 to 72 hours before the eye surgery were also excluded.

The study was conducted in the Department of Ophthalmology, University of São Paulo, São Paulo, Brazil,

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from April to May 2014, and it received prospective approval from the institution's Ethics Committee, Brazil Review Board (#24259613.3.0000.0068).

Preoperative ophthalmic examination included uncorrected visual acuity, best spectacle-corrected visual acuity using the Snellen visual acuity chart, manifest and cycloplegic refraction, corneal tomography (Orbscan II; Bausch & Lomb, Rochester, NY), and indirect ophthalmoscopy. No eye had ocular abnormalities other than refractive error, and no eye had previously undergone ocular surgery. All patients had both eyes operated on at an interval of 14 days, and the laterality was randomly assigned. Subjects answered Spielberger's[16] State Anxiety Inventory (SAI) 1 hour before the surgery.

After topical anesthesia was applied (tetracaine hydrochloride 0.5% drops), the corneal epithelium was removed after exposure to 20% ethanol diluted with balanced salt solution (BSS) instilled in a 9-mm optical zone for 20 seconds. Using a cellulose sponge, the ethanol solution was absorbed, followed by copious irrigation with balanced salt solution. Surgery was performed by the same surgeon using the NIDEK EC-5000CXIII scanning excimer laser system. Ablation/transition zones were the same for all patients. Mitomycin C was not used in this study.

After surgery, an etafilcon A (Johnson & Johnson Vision Care, Inc.) contact lens was placed over the cornea and left until complete corneal reepithelialization was achieved. All eyes had their contact lens removed after 96 hours or longer. Patients were treated with topical nepafenac (0.1%), moxifloxacin (0.5%), and dexamethasone (0.1%) 4 times daily for 5 days, as well as 200 mg of celecoxib 2 hours before surgery and then daily for 4 days after surgery. Topical dexamethasone (0.1%) was slowly tapered in 2 months. All participants responded to the Visual Analog Scale (VAS), Brief Pain Inventory (BPI), and McGill Pain Questionnaire (MPQ) at 1, 24, 48, 72, and 96 hours after surgery. One interviewer administered the questionnaires in a randomly assigned order.

Garcia et al[6] have demonstrated the reliability, validity, and ability to detect changes in pain using the BPI and MPQ in the postoperative period after PRK.

The preoperative information and knowledge about the procedure was considered to be PRK on the first eye, which occurred 14 days before PRK on the second eye. The same surgeon performed all surgeries in a similar surgical environment, temperature, and humidity.

Pain Questionnaires

VAS

The pain VAS is a 1-dimensional measure of pain intensity that has been widely used in diverse adult populations, including ophthalmology patients. The VAS rating is based on a total score of 0 to 10.[17]

BPI

The BPI consists of a questionnaire with 11 items. It was designed to evaluate the intensity of pain and the related impairment in the previous 24 hours. The BPI was previously translated into Brazilian Portuguese and validated.[18] The BPI items are aggregated into 2 dimensions: (1) the Pain Severity Index (PSI), using the sum of the 4 items on pain intensity, and (2) the Function Interference Index (FII), using the sum of the 7 pain interference items. The PSI and FII ratings are based on a total score of 0 to 40 and 0 to 70, respectively.[19]

MPQ

The MPQ is a multidimensional pain questionnaire designed to measure the sensory, affective, and evaluative aspects of pain. It was previously translated into Brazilian Portuguese and validated.[20] The MPQ questionnaire contains 4 subscales evaluating the sensory, affective, evaluative, and miscellaneous aspects of pain, the sum of which comprises the Pain Rating Index (PRI). The PRI, PRI sensory, affective, evaluative, and miscellaneous ratings are based on a total score of 0 to 78, 0 to 42, 0 to 14, 0 to 5, and 0 to 17, respectively.[21]

Anxiety Questionnaire

Spielberger's SAI

The SAI is a well-known instrument that is the gold standard for anxiety evaluation, and it was validated and adapted to Brazilian Portuguese.[22] The SAI is a 20-item questionnaire that provides measures of state of anxiety, where higher scores indicate greater anxiety levels. In our study, the levels of anxiety were assessed 1 hour before surgery. Respondents were asked to rate themselves on each item on the basis of a 4-point scale, ranging from (1) not at all, (2) somewhat, (3) moderately, and (4) very much so. The total score for each scale ranged from 20 to 80.[16]

Statistical Analysis

All statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL). A P value <0.05 was considered statistically significant. The Kolmogorov–Smirnov

TABLE 1. Demographic Characteristics

Variables	Description (N = 43)
Race, n (%)	
White	38 (88.4%)
Asian	1 (2.3%)
Black	4 (9.3%)
Education, n (%)	
High school	9 (20.9%)
College	34 (79.1%)
Sex, n (%)	
Male	22 (51.2%)
Female	21 (48.8%)
First eye operated, n (%)	
Right	23 (53.5%)
Left	20 (46.5%)
Age, yrs	
Mean (SD)	30.6 (4.4)
Median (min; max)	30 (22; 43)

SD, standard deviation; min, minimum; max, maximum.

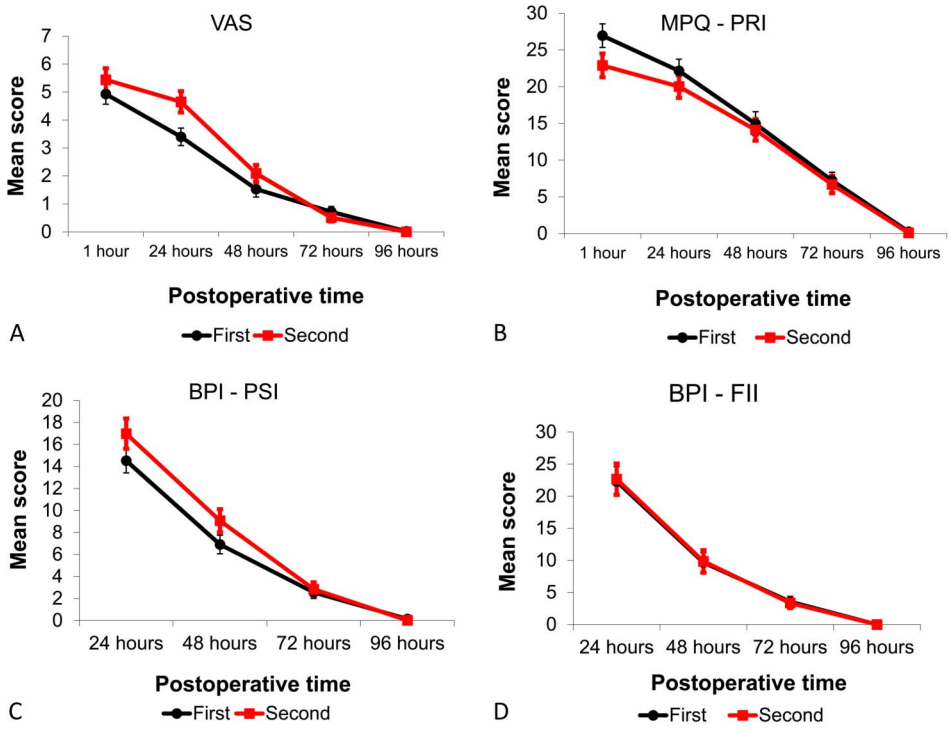

FIGURE 1. Postoperative PRK pain curves and the standard errors of each operated eye with the (A) the VAS, (B) the McGill Pain Rating Index, (C) the BPI–PSI, and (D) the BPI–FII.

test was used to confirm the normal distribution of scales at all times in each eye.

The VAS pain score variability at the moment of the greatest ocular pain after PRK had average values of 2 points in other studies[23,24] and in our pilot study. A power calculation indicated that a study with 32 pairs of eyes was required to detect a maximum of 2 units of difference in VAS pain scores between the first and second eyes that were operated on with 80% statistical power and 95% confidence level. Therefore, 43 subjects were sufficient for the purpose of this study with consideration of study withdrawals and losses to follow-up. We could compare pain profiles between both eyes, the influence of the information acquired during the first surgery on the pain profile of second-eye surgery, and the effect of anxiety in both eyes.

For secondary aims, we have performed analysis for each eye separately. The average pain results for gender and SERE according to the VAS, BPI, and PRI with a confidence interval of 95% showed satisfactory precision.

The database of the first and second eyes that were operated on was used in this study. Quantitative personal characteristics were described using summary measures (mean, SD, median, minimum, and maximum), and the qualitative characteristics evaluated in patients were reported with using absolute and relative frequencies. The scale and subscale data collected from the pain assessment questionnaires are presented as the mean and SD at each postoperative observation period for each eye.

The pain scales and subscales were compared between the first and second eye that was operated on at each time point studied using generalized estimating equations of the Wald test with a first-order autoregressive correlation matrix with a normal marginal distribution and identity link function. For significant statistical models, we used Bonferroni multiple comparisons tests to compare different postoperative periods to determine if there were differences in scales and subscales between each eye and each time point. The same statistical method was used to analyze pain scales, gender, and SERE.

A paired Student *t* test was used for comparing SERE and SAI between both eyes. The Pearson correlation coefficients were calculated among the SAI with the scales and subscales at each time point to determine whether these psychometrics and the psychological properties could potentially predict pain profiles.

TABLE 2. Spherical Equivalent Refractive Error and Anxiety Between Both Eyes of Subjects in Comparative Tests

Variables	Classification Eye	Average	SD	Median	Minimum	Maximum	N	*P*
SERE (D)	First	−2.5	0.9	−2.3	−1	−5	43	0.514
	Second	−2.4	0.9	−2.3	−1	−5	43	
SAI	First	31.3	8.5	29	20	52	43	**<0.001**
	Second	25.6	6.1	23	20	45	43	

Paired Student *t* test results for the Spherical Equivalent Refractive Error (SERE) and State Anxiety Inventory (SAI).

TABLE 3. Correlation Between Pain Scales and SAI for Each Eye

	SAI	
Correlation	**First Eye**	**Second Eye**
VAS		
1 h		
r	−0.252	0.089
P	0.104	0.569
24 h		
r	0.039	0.052
P	0.803	0.739
48 h		
r	−0.061	0.089
P	0.696	0.570
72 h		
r	0.092	−0.031
P	0.558	0.842
96 h		
r	−0.078	#
P	0.619	
BPI–PSI		
24 h		
r	−0.089	0.199
P	0.572	0.202
48 h		
r	−0.017	0.298
P	0.916	0.052
72 h		
r	0.047	0.105
P	0.765	0.503
96 h		
r	−0.015	0.498
P	0.926	**0.001**
BPI–FII		
24 h		
r	−0.020	0.323
P	0.899	**0.035**
48 h		
r	−0.072	0.486
P	0.645	**0.001**
72 h		
r	−0.025	0.070
P	0.874	0.656
96 h		
r	#	#
P		
MPQ–PRI		
1 h		
r	−0.200	0.073
P	0.199	0.647
24 h		
r	0.108	0.220
P	0.490	0.161
48 h		
r	−0.016	0.323
P	0.918	**0.037**
72 h		
r	0.113	0.108
P	0.471	0.497
96 h		
r	−0.046	0.412
P	0.769	**0.007**
MPQ–PRI evaluative		
1 h		
r	−0.227	−0.077
P	0.143	0.628
24 h		
r	−0.163	−0.096
P	0.296	0.545
48 h		
r	−0.052	0.216
P	0.742	0.169
72 h		
r	0.054	0.229
P	0.729	0.144
96 h		
r	−0.078	0.511
P	0.619	**0.001**

Pearson values.

SAI, State Anxiety Inventory; #, no values detected at this time; VAS, Visual Analog Scale; BPI-PSI, Brief Pain Inventory-Pain Severity Index; BPI-FII, Brief Pain Inventory-Function Interference Index; MPQ PRI, McGill Pain Questionnaire-Pain Rating Index; MPQ PRI Evaluative, McGill Pain Questionnaire-Pain Rating Index Evaluative; SAI, State Anxiety Inventory.

RESULTS

Forty-three patients who fulfilled the inclusion criteria participated in the study and completed the full postoperative 5-day evaluation. Table 1 provides the demographic characteristics of subjects. The mean patient age was 30.6 ± 4.4 years, and 51% of the patients were male.

Figure 1 shows the average scores for postoperative pain after PRK for each eye. There were no statistically significant differences between both eyes for all time points that were analyzed with the VAS, MPQ–PRI, BPI–PSI, and BPI–FII. The same results were revealed by the generalized estimating equations of the Wald test.

As shown in Table 2, patients were less anxious on average before the second surgery compared to before the first surgery ($P < 0.001$). The SERE average was statistically similar for both eyes ($P = 0.514$).

Anxiety level before the surgery was not related to pain ratings after surgery for almost all time points, as demonstrated by the Pearson values in Table 3.

After applying the Wald test, we found that gender did not significantly interfere with any scale of pain ($P > 0.05$). Interestingly, SERE showed interference on the BPI–PSI. The average pain score on the BPI–PSI was higher in patients with

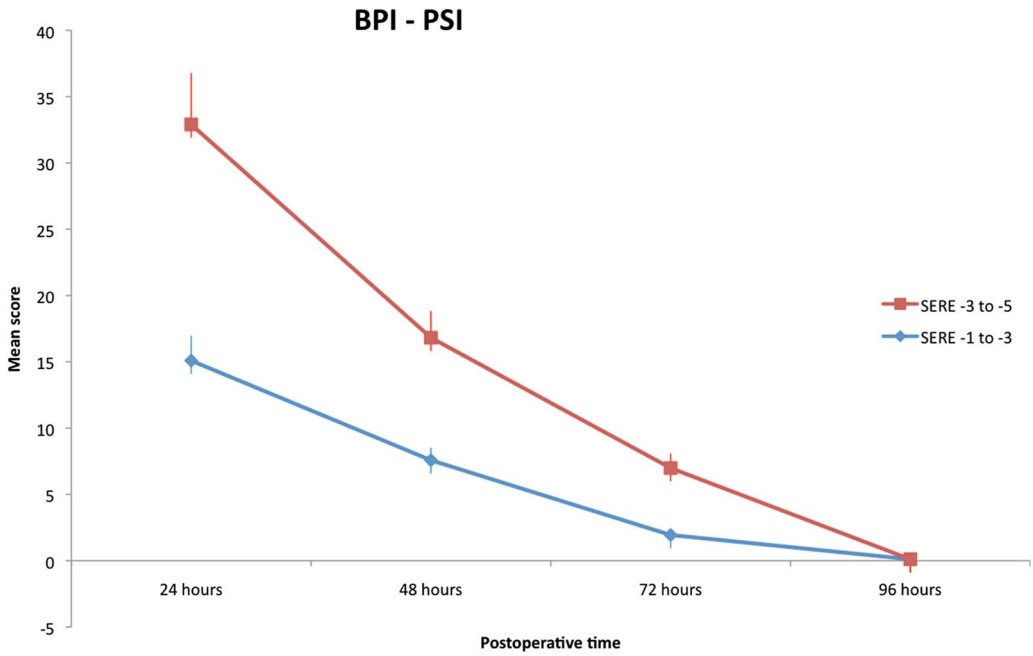

FIGURE 2. Postoperative PRK pain curves and the standard errors of each operated eye with the BPI–PSI for a SERE of -1D to -3D and a SERE of -3D to -5D.

a SERE between −3 D and −5 D ($P = 0.035$) independent of the postoperative evaluation time point (Fig. 2).

DISCUSSION

Surgery is a high-stress situation that evokes intense emotional reactions and involves considerable physical danger, and it may be quite painful. The identification of patients at high risk could help to initiate individual effective treatment strategies at an early stage to prevent severe pain. In the current study, some traditional preoperative predictors of postoperative pain were tested for the first time in PRK.

Several published noneye studies have demonstrated that the state of anxiety is a significant, positive linear predictor of postoperative pain.[9,25] These studies suggest that anxiety may potentiate pain because patients become more attentive.[26,27] As demonstrated in Table 2, the average score of the SAI before surgery on the second eye was statistically significantly lower than the score of the SAI before surgery on the first eye ($P < 0.001$). Subjects were more anxious before the first-eye surgery, most likely due to the fear of the unknown. However, the correlations between the SAI and pain scales were not statistically significant ($P > 0.05$) at almost all time points. Thus the state of anxiety did not influence the perceived pain. It is known that the majority of PRK surgeries are performed bilaterally on the same day, and our findings support the current practice as concerning postoperative pain.

There have been few studies in the literature comparing patients' pain experiences between first-eye surgery and second-eye surgery in ophthalmology. Sharma et al[28] studied patients' recall of intraoperative pain, anxiety, and sensory perceptions during second-eye cataract surgery compared with first-eye cataract surgery using the same technique, topical anesthesia, and intravenous sedation. They found no statistically significant difference between first-eye and second-eye procedures. A more recent study by Ursea et al[29] yielded different results, finding less anxiety and more pain during second-eye cataract extraction. Rami et al[30] compared pain scores during laser in situ keratomileusis between first-eye surgery and second-eye surgery and found a significantly higher degree of subjective pain during second-eye surgery. The reason pain perception was significantly higher during second-eye surgeries was unclear to them. The authors suggested that the subjects seemed less anxious and more relaxed during the second-eye surgery, which might heighten any pain perception.[30] A few reports indicated that information can sensitize the patient to experience more pain.[31,32] Therefore, there are contradictory findings about the influence of preoperative information and knowledge on postoperative pain. An often-cited study from 1964[33] reported that the group receiving information about pain and postoperative recovery experienced less pain than the control group. Many studies have shown that preoperative information is considered to be an important tool in helping patients reduce the anxiety associated with surgery.[34,35] In our study, the reduced anxiety state before PRK of the second eye reinforced this theory.

It was expected that the information acquired during the surgery on the first eye would help to significantly reduce the levels of pain during the surgery on the second eye. As shown in Figure 1, there were no statistically significant differences in pain scores at almost all time points of evaluation. The generalized estimating equations of the Wald test also demonstrated similar behavior of the scales for both eyes that were operated on for all evaluated time periods.

If we consider the significantly reduced state of anxiety and the information effect of the procedure, we would expect to have at least 2 reasons for significantly reduced scores of pain postoperatively after PRK of the second eye, which did not occur.

Another important preoperative predictor of postoperative pain that has been reported in the literature is the gender of the subjects.[11,12] The influence of gender has been intensively studied, although its role in pain sensitivity is still unclear. Evidence of physiological or hormonal factors that may contribute to sex differences in pain sensitivity has not been found or is inconsistent.[36]

There are also contradictory findings regarding the influence of gender on postoperative pain. Some reports indicate that women and men experience pain very differently.[37,38] It has been proposed that women may be more sensitive to deep tissue pain, which has been used as a partial explanation for the higher prevalence of musculoskeletal pain disorders in women.[39]

Some ophthalmologic studies concluded that there was no significant difference in postoperative pain scores between men and women.[40,41] In agreement, our study suggested that gender did not interfere in any pain scale during the postoperative period after PRK. On the other hand, Henzler et al[42] found that women experienced more pain than men.

A specific variable applied to PRK that is supposed to increase the risk of pain after surgery is the excimer laser quantity used in corneal ablation. It is well known that higher refractive errors are associated with larger quantities of laser and deeper ablation. Consequently, there is a higher risk of haze when high refractive errors are treated.[15] In our study, the pain average in the BPI–PSI was higher in patients with a SERE between −3 D and −5 D than in patients with a SERE between −1 D and −3 D at all postoperative time periods. This finding is supported by the mechanisms of corneal pain after PRK. Interestingly, there was no statistically significant correlation between the SERE and MPQ–PRI. The BPI and MPQ–PRI are multidimensional questionnaires that evaluate different aspects of pain. One questionnaire adds information to another. Thus, most likely some subjective aspect of pain was better assessed by the BPI questionnaire.

There are some limitations to our study. First, the memory factor can interfere with the levels of anxiety and pain.[30] We decided on a 14-day interval between the eye surgeries to try to eliminate any influence of the first-eye surgery on the second-eye surgery. A longer interval would be uncomfortable because of anisokonia between the eyes. Second, the different individual responses to nonsteroidal antiinflammatory drugs and analgesics based on genetic factors contribute to individual variation in pain sensitivity.[43] Another possible limitation could be the absence of analyses of social and ethnic characteristics of the subjects. Conditions such as unemployment, religion, and race could interfere with anxiety and pain perception.

Our findings show that variables such as gender, information regarding the surgical process, and the state of anxiety are not good predictors of the risk of severe pain after PRK. This study suggests that a high SERE is a risk factor for increased pain after PRK. The profiles of postoperative pain after PRK were similar between both eyes under the same conditions. We believe that the identification of other predictors of pain after PRK in addition to the SERE may be useful for providing more effective approaches to control pain and may enable their widespread use for treatment.

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