Post-photorefractive Keratectomy Pain and Corneal Sub-basal Nerve Density

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Abstract

Purpose: The perceived and reported pain of patients receiving photorefractive keratectomy (PRK) widely varies. We assessed the potential role of the subbasal nerve plexus density as a predictor of postoperative pain level. Consecutive patients scheduled to undergo PRK at the Refractive Surgery Clinic of Farabi Eye Hospital, Tehran, were approached.

Methods: Forty-nine myopic left eyes from 49 patients who consented to undergo scanning slit confocal microscopy assessments preoperatively were included. ImageJ (1.48v) was used to measure the captured subbasal nerve length. Postoperative pain intensity was assessed by the Visual Analog Scale (VAS) (score range: 0 for no pain to 10 for the maximum possible) on the next day of surgery.

Results: The mean age of the patients was 27.55 (range: 19–40) years. The median reported pain level was 5. Approximately 32.7% of the subjects reported a pain score of 6 or higher. Mean nerve density was 19.54 (range: 14.34–24.73) mm/mm². Nerve density was not correlated with the reported intensity of pain (P = 0.172). However, pain was correlated with the reported ocular discomfort, i.e., a pooled index of foreign body sensation, photophobia, burning sensation, and tearing (P < 0.001), and also with the pooled index of ocular inflammatory signs (conjunctival injection and eyelid edema) (P = 0.027).

Conclusion: Crude density of corneal nerves may not be a good predictor of post-PRK pain while wearing bandage contact lenses. The predominant pain mechanism appears to be of an inflammatory nature (not nociceptive or neuropathic).

Keywords: Corneal Subbasal Nerve Density; In vivo confocal Scan; Photorefractive Keratectomy; Postoperative Pain

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INTRODUCTION

The incidence of postoperative pain is a common and major challenge after photorefractive keratectomy (PRK). [1-3]

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Limited research has been conducted to identify the possible risk factors of post-PRK pain. [1,4] It is hypothesized that the exposure of the corneal nerve endings, as a result of PRK, is responsible for the symptoms of intense pain. [5] This suggests that there is a relationship between corneal subbasal nerve density and pain after PRK. Nerve density can be measured in vivo, quantitatively, with confocal microscopy. Confocal microscopy has become

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a popular method over the last decade for investigating diseases of the eye and has allowed for significant breakthroughs.\textsuperscript{[6]}

The purpose of this study was to evaluate the relationship between the incidence of pain after PRK and the corneal subbasal plexus nerve density, external ocular signs of inflammation, and patient reported ocular discomfort.

**METHODS**

**Participants**

Patients who underwent PRK at the Refractive Surgery Clinic of Farabi Eye Hospital, Tehran, were consecutively included. The study protocol was reviewed and approved by the Institutional Review Board of Farabi Eye Hospital. The participants provided informed, written consent to be examined with Confoscan (HRT3, Heidelberg eye explorer, version 1.7.0.0).

We excluded patients who were younger than 18 and those who were over 40 years old, in addition to patients with corneal pathologies, a history of previous eye surgery and systemic diseases, a spherical equivalent more than 6.0 diopters (D) and astigmatism more than 3.0 D.

In addition to the standard preoperative examinations, the patients underwent \textit{in vivo} confocal microscopy, and they were interviewed on their social habits (smoking, drug, and alcohol use) and contact lens wear routines. Height and weight were measured to calculate body mass index (BMI).

**In-vivo Confocal Microscopy**

\textit{In vivo} confocal microscopy was performed on the central cornea of the patients’ left eyes using the Heidelberg Retina Tomograph III (HRT3) and the Rockstock Cornea Module (RCM) (Heidelberg Engineering, Germany). For this purpose, a large drop of high viscosity contact gel was applied on the front surface of the microscope lens and a sterile Tomocap (Heidelberg Engineering, Germany) was mounted to cover the microscope lens. Subsequently, a drop of topical anesthetic was instilled into the eye. Following the engagement of the machine probe onto the corneal surface, image capturing from the central cornea was carried out. The area of interest consisted of the subbasal nerve fiber plexus, which appeared at a depth of 40–60 \( \mu \text{m} \). The focus level was changed manually in the axial direction. Sequential images were captured at this level from the central areas of the cornea. Each eye examination took an average of 5 minutes to complete.\textsuperscript{[6‑9]}

**Image Analysis**

The images were studied by a trained observer (KAA) who selected two images for each eye. The selection criteria included an absence of motion or pressure induced artifacts, in addition to high contrast with clear delineation from the background.\textsuperscript{[6]}

Corneal subbasal nerves were manually traced in each image, guided by NeuronJ plug-in ImageJ delineation software [Figure 1]. Total nerve length was calculated and divided by the total corneal area in each image (384 \( \times \) 384 \( \mu \text{m}^2 \)). This yielded the subbasal nerve density in each central cornea (mean nerve density of the two images for each eye was used).

**Surgical Procedure**

A single surgeon (MM) performed the surgeries following a conventional technique using 75-degree alcohol for epithelial debridement. A nominal optical zone of 6 mm was set and the ablation was performed under the Zyoptix Tissue Saving protocol of the Technolas 217P excimer laser (Technolas Perfect Vision GmbH, Munich, Germany). In addition to topical steroids and prophylactic antibiotics, patients were prescribed standard and identical doses of analgesics and were instructed on how to take them to ensure inter-patient consistency.

**Postoperative Visit**

The patients had a follow-up visit the next day after surgery (18-24 hours postoperatively). To survey the incidence of patient discomfort since the operation, the patients were queried and graded on a scale of 0 to 2 for the following items: degree of foreign body sensation, incidence of photophobia, burning sensation and tearing. The incidence of pain in the left eye since surgery was measured using the visual analog scale (VAS), and patients were asked to score their pain from 0 (no pain) to 10 (maximum). We inspected the patients’ left eyes for lid edema and conjunctival injection, and scored them separately on a scale of 0 to 2.

![Figure 1. Tracing of the corneal subbasal nerve. The original image (right) and the traced image (left), which was produced using NeuronJ, are depicted.](image-url)
Data Analysis

We used SPSS version 17 for statistical analysis. Spearman test was used for evaluating the correlation between nerve density ocular discomfort indices and the proxies of inflammation. We analyzed the possible association between nerve density and the patients’ pain score with the patients’ sex, age, BMI, contact lens wear routine, and social habits.

Owing to the ordinal nature of pain and other discomfort scales, we calculated the Spearman correlation coefficient with nerve density. We did not average the pain scores and provided the median rather than the mean. For the statistical analysis of pain data, we used non-parametric tests only.

For the sake of sensitivity analysis, we excluded the contact lens wearers subset and reanalyzed the data.

RESULTS

A total of 52 left eyes from 52 patients were enrolled in the study. Two patients were excluded due to the incidence of corneal scarring and one was excluded due to low image quality. The mean age of the remaining 49 patients was 27.55 (range, 19 to 40) years and 27 patients (55.1%) were female. Mean spherical equivalent refraction was −3.05 D (range, −0.75 to −5.5 D), and the cylindrical power ranged from −3 to +3. Mean BMI was 24.35 (range, 17.44 to 31.14) kg/m².

We traced the subbasal corneal nerves in 98 Confoscan images (2 images per eye). Nerve density was calculated as the total length of the visible subbasal nerves in each frame divided by the total area of the frame (384 × 384 μm²). Mean nerve density was 19.54 ± 2.96 mm/mm², following a normal distribution [Figure 2].

The median pain score for VAS was 5, and 32.7% (16/49) of the patients reported a pain score of 6 or higher. No significant relationship was observed between nerve density and pain score. Pain score correlated with reported ocular discomfort, i.e., a pooled index of foreign body sensation, photophobia, burning sensation, and tearing (P < 0.001) and also correlated with the pooled index of external ocular inflammatory signs (conjunctival injection and eyelid edema) (P = 0.027).

For the sensitivity analysis, we excluded the contact lens wearers subset and reanalyzed the data. No changes were observed.

We tested the relationship between contact lens wear and the severity and incidence of pain using a Mann-Whitney U test. Pain was not correlated with contact lens wear history (pain scores were 24.5 and 25.5 for contact lens wearers and non-wearers, respectively).

Neither the pain score nor the nerve density significantly correlated with other studied variables such as ablation depth, spherical equivalent refraction, age, sex, history of contact lens wear, social habits, or BMI.

DISCUSSION

Our patients reported post-PRK pain ranging from 0 to 10 with a median of 5 for VAS. The median post-PRK pain score in the study by Mohammadi et al was 3 and a mean score of 5 was reported by Shoratt et al in 2008 using the same scale. We were unable to show evidence of a relationship between pain and nerve density; nonetheless, the pain score was correlated with postoperative ocular symptoms and signs (foreign body sensation, burning, tearing, photophobia, lid edema, and conjunctival injection). It should be noted, however, that these indices were not easily separable. To address this issue, we calculated the pooled scores. There was no significant relationship evident between nerve density and the pooled estimates.

Pain is a major entity in medicine and is an extremely heterogeneous condition that can be described as acute, chronic, aching, dull, throbbing, referral, stabbing, excruciating, etc. It can be either symptomatic of a disease or be experienced postoperatively. Corneal pain, similar to the incidence of pains elsewhere in the body, has at least three pathophysiologic subtypes, i.e., inflammatory, nociceptive, and neuropathic.

Our evidence supports each of the aforementioned mechanisms in post-PRK pain for which topical and systemic anti-inflammatory agents (steroidal and non-steroidal) were administered. These agents were shown to reduce the patient’s perception of pain. Our pooled index for external eye inflammation showed a significant association with pain (P = 0.027), which provides evidence for the pathophysiologic role of inflammation during postoperative pain.

Nociceptive pain, which is mediated by the activity of the exposed nerve fibers in the injured tissue,
appears to be the most relevant to corneal subbasal nerve density. To alleviate this type of pain, we used bandage contact lenses, which dramatically control and effectively alleviate excruciating pain.\textsuperscript{14} As an alternative for contact lenses, we can apply tight eye patching to keep the eyelid from rubbing over the injured surface and severed nerve endings. We believe that applying bandage contact lenses might have nullified our key hypothesis i.e., the association of post-PRK pain with nerve density.

The third mechanism, which is neuropathic pain, is mostly related to chronic conditions such as dry eye disease. There is conflicting evidence about the pathophysiologic role of this type of pain following PRK. The oral anti-neuralgic (anti-seizure) agent, ‘Gabapentin’, has been shown to provide symptomatic alleviation of pain, but the results were rather inconsistent.\textsuperscript{3}

We explored the association of non-pain symptoms with pain and observed that there was a significant relationship ($P < 0.001$). Nonetheless, the patients could not delineate between the subjective experiences of discomfort, such as burning sensations, pain, photophobia, stinging, etc. Therefore, we occasionally use the blanket title, ‘ocular discomfort’, instead. However, none of the symptoms were associated with nerve density.

The cornea is the most densely innervated tissue in the body. The concentration of nerve endings is 200 to 300 times greater than that of the skin,\textsuperscript{15} which explains the extreme sensitivity and pain sensation of the cornea. Current research attributes an increasingly greater role to nerve density for ocular surface health, i.e., tear film function and corneal wound healing. Additionally, nerve density decreases following keratorefractive surgeries, in ocular herpes,\textsuperscript{16,17} and in diabetic neuropathy.\textsuperscript{18-20} Chronic contact lens wear has also been shown to decrease nerve density, and this is accompanied by corneal hypoesthesia for contact lens wearers. Interestingly, this has been shown to be a reversible process. As mentioned, we could not demonstrate an association between contact lens wear and post-PRK pain. In fact, in our study cohort, lens wear was not common and only 22.4% of the patients had a lens wear history.

\textit{In vivo} confocal microscopy has been instrumental for elucidating the mechanisms of pain and its associations. The mean nerve density in our myopic cases was comparable to that of emmetropes in previous studies.\textsuperscript{6}

BMI was shown by Mohammadi et al.\textsuperscript{11} to positively correlate with pain, and this was attributed to using standard oral analgesics without adjusting the dosage to the body mass of the individual patients. They also demonstrated a relationship between smoking and the incidence of pain. This was not replicated in the current study. In order to better assess the role of individual factors on post-PRK pain, studies with larger sample sizes are needed.

We questioned the patients specifically about the pain in their left eye; nonetheless, it is debatable if pain can be differentiated between the right and the left eye, and from overall discomfort. However, this feature was not selective and did not influence the result.

The prevalence of postoperative discomfort following second eye surgery has been reported to be higher, but this appears to be unrelated in the present study, as we performed PRK consecutively without an interval (which is the routine procedure for second eye surgery). Moreover, the results would have been unaffected as the same procedure was performed for all cases, and was performed in the left eye.

In conclusion, we could not show a relationship between subbasal nerve density and pain or other symptoms of ocular discomfort after PRK. The authors believe that bandage contact lens wear after PRK could conceal such an association. We replicated the relationship of post-PRK pain and ocular surface inflammatory signs.

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\section*{Conflicts of Interest}

There are no conflicts of interest.

\section*{REFERENCES}

1. Mohammadi SF, Z Mehrjardi H, Vakili ST, Majdi M, Mirhadi S, Rahimi F. Pain and Its Determinants in Photorefractive Keratectomy. Asia Pac J Ophthalmol (Phila) 2012;1:336-339.
2. Woreta FA, Gupta A, Hochstetler B, Bower KS. Management of post-photorefractive keratectomy pain. Surv Ophthalmol 2013;58:529-535.
3. Fagerholm P. Wound healing after photorefractive keratectomy. J Cataract Refract Surg 2000;26:432-447.
4. Melki SA, Azar DT. LASIK complications: Etiology, management, and prevention. Surv Ophthalmol 2001;46:95-116.
5. Villani E, Baudouin C, Efron N, Hamrah P, Koijima T, Patel SV, et al. \textit{In vivo} confocal microscopy of the ocular surface: From bench to bedside. Curr Eye Res 2014;39:213-231.
6. Parissi M, Karanis G, Randjelovic S, Gernundsson J, Poletti E, Ruggeri A, et al. Standardized baseline human corneal subbasal nerve density for clinical investigations with laser-scanning \textit{in vivo} confocal microscopy. Invest Ophthalmol Vis Sci 2013;54:7091-7102.
7. Erie EA, McLaren JW, Kittleson KM, Patel SV, Erie JC, Bourne WM. Corneal subbasal nerve density: A comparison of two confocal microscopes. Eye Contact Lens 2008;34:322-325.
8. Zhivov A, Winter K, Peschel S, Stachs O, Wree A, Hildebrandt G, et al. Changes in the micromorphology of the corneal subbasal nerve plexus in patients after plaque brachytherapy. Radiat Oncol 2013;8:136.
9. Tavakoli M, Hossain P, Malik RA. Clinical applications of corneal confocal microscopy. *Clin Ophthalmol* 2008;2:435-445.

10. Shortt AJ, Allan BD, Evans JR. Laser-assisted in-situ keratomileusis (LASIK) versus photorefractive keratectomy (PRK) for myopia. *Cochrane Database Syst Rev* 2013;1:CD005135.

11. Belmonte C, Acosta MC, Merayo-Lloves J, Gallar J. What Causes Eye Pain? *Curr Ophthalmol Rep* 2015;3:111-121.

12. Fay J, Juthani V. Current trends in pain management after photorefractive and phototherapeutic keratectomy. *Curr Opin Ophthalmol* 2015;26:255-259.

13. Schaible HG, Richter F. Pathophysiology of pain. *Langenbecks Arch Surg* 2004;389:237-243.

14. Taylor KR, Caldwell MC, Payne AM, Apsey DA, Townley JR, Reilly CD, et al. Comparison of 3 silicone hydrogel bandage soft contact lenses for pain control after photorefractive keratectomy. *J Cataract Refract Surg* 2014;40:1798-1804.

15. Kumar RL, Cruzat A, Hamrah P. Current state of *in vivo* confocal microscopy in management of microbial keratitis. *Semin Ophthalmol* 2010;25:166-170.

16. Cottrell P, Ahmed S, James C, Hodson J, McDonnell PJ, Rauz S, et al. Neuron J is a rapid and reliable open source tool for evaluating corneal nerve density in herpes simplex keratitis. *Invest Ophthalmol Vis Sci* 2014;55:7312-7320.

17. Hamrah P, Cruzat A, Dastjerdi MH, Pruss H, Zheng L, Shahatit BM, et al. Unilateral herpes zoster ophthalmicus results in bilateral corneal nerve alteration: An *in vivo* confocal microscopy study. *Ophthalmology* 2013;120:40-47.

18. Misra S, Ahn HN, Craig JP, Pradhan M, Patel DV, McGhee CN. Effect of panretinal photocoagulation on corneal sensation and the corneal subbasal nerve plexus in diabetes mellitus. *Invest Ophthalmol Vis Sci* 2013;54:4485-4490.

19. Malik RA, Kallinikos P, Abbott CA, van Schie CH, Morgan P, Efron N, et al. Corneal confocal microscopy: A non-invasive surrogate of nerve fibre damage and repair in diabetic patients. *Diabetologia* 2003;46:683-688.

20. Mocan MC, Durukan I, Irkec M, Orhan M. Morphologic alterations of both the stromal and subbasal nerves in the corneas of patients with diabetes. *Cornea* 2006;25:769-773.