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Evaluation of early postoperative ocular pain after photorefractive keratectomy and corneal crosslinking

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Purpose: To evaluate and compare early postoperative pain after photorefractive keratectomy (PRK) and corneal crosslinking (CXL).

Setting: Khatam-al-Anbia Eye Hospital, Mashhad, Iran.

Design: Prospective case series.

Methods: The PRK group included patients with simple refractive errors whereas the CXL group included patients with clinical keratoconus. The groups were compared regarding the level of pain based on the visual analogue scale (VAS), verbal rating scale (VRS), and Wong-Baker FACES pain rating scale immediately after surgery, 6 hours postoperatively, and 1, 3, and 7 days postoperatively. The epithelial defect size was measured at 6 hours after surgery and 1 day and 3 days after surgery in both groups.

Results: The study comprised 68 patients (34 patients in the PRK group and 34 patients in the CXL group). The epithelial defect size was significantly smaller in the CXL group than in the PRK group ($P < .001$); however, the amount of pain was significantly higher after CXL than after PRK based on VAS and VRS ($P = .04$ and $P = .019$, respectively). In the FACES scaling system, the pain score was also higher in the CXL group than in the PRK group. However, the difference was not statistically significant. No intraoperative or postoperative complications were observed during follow-up.

Conclusions: The epithelial defect healing rate was statistically significantly faster in the CXL group than in the PRK group. However, the level of pain was greater in the CXL group, suggesting that postsurgical pain might be influenced by other factors than the epithelial defect.

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The cornea has the densest small fiber innervation in the body. The corneal nerve density is estimated to be 300 to 400 times higher than that of human skin.[1,2] Corneal sensory nerve fibers containing myelinated Aδ and unmyelinated C fibers, which are derived from the ophthalmic branch of the trigeminal nerve, penetrate the limbus and form a rich subepithelial nerve plexus in the anterior third of the stroma.[2–5] This nerve plexus brings the pain signals to the central nervous system.

Several mechanisms might be involved in cornea-related pain, including stimulation of the corneal nerve endings from an epithelial defect, ablation of corneal nerves, and chemoactivation of nerves by neuromediators and chemicals.[6–9] The exact mechanism of cornea-related pain is still unclear and patients might experience intensive pain after corneal procedures.

Since the introduction of corneal crosslinking (CXL) and photorefractive keratectomy (PRK) procedures, postoperative pain management has been a major challenge for both the patient and the surgeon.

Corneal crosslinking is a promising procedure to halt the progression of keratoconus.[6,9,10] Corneal crosslinking uses ultraviolet-A (UVA) light and riboflavin (a photosensitizer), which strengthens the cornea by releasing oxygen radicals that lead to covalent crosslinking of the collagen fibers.[9–12] The postoperative pain can be intense, in particular in the first 3 days, even with an aggressive pain control regimen.[13,14]

Corneal surface ablation, in the form of PRK, has long been a mainstay for the treatment of refractive errors such as myopia.[7] A considerable portion of the anterior cornea containing heavy innervation is removed in this

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procedure and patients often experience severe pain and discomfort.[2,3,8]

In both procedures, an epithelial defect persists for several days, which can result in severe pain. However, it seems these procedures might elicit pain through different pathways. Photorefractive keratectomy removes anterior stromal tissue containing heavy innervation and thus damages the subbasal nerve plexus and anterior stromal nerves, whereas with CXL, the Bowman layer and stroma are not disrupted; however, oxidative stress is induced by the photochemical reaction of riboflavin and UVA along with the release of free oxygen radicals in the corneal stroma and might lead to pain sensation in the presence of the intact subbasal nerve plexus.

To our knowledge, no study so far has evaluated and compared the pain in the early postoperative period after these 2 surgeries. Therefore, in the current study, we aimed to compare the level of pain and discomfort along with the rate of epithelial healing after application of these 2 widely used surgical techniques to foster an improved understanding of cornea-related pain.

PATIENTS AND METHODS

Study Population

In this prospective clinical study, patients who had bilateral same-day CXL or bilateral same-day PRK were included. After fully describing the surgical protocol, an informed consent was obtained from each participant before study entrance. The study protocol was approved by the Ethics Committee of the University of Medical Sciences. All study procedures adhered to the tenets of the Declaration of Helsinki.

Study Design

The inclusion criteria for the PRK group were a refractive error of −1.0 to −6.0 diopters (D) myopia and less than 2.0 D astigmatism that had been stable for at least 1 year and no contraindication to refractive surgery such as clinical keratoconus or keratoconus suspect as confirmed by corneal imaging. The inclusion criteria for the CXL group included clinically progressive keratoconus and minimum corneal thickness greater than 400 µm. The exclusion criteria included any other ocular comorbidity such as a previous corneal ulcer, ocular herpetic disease, glaucoma, or systemic conditions such as autoimmune diseases, collagen-vascular disease, diabetes mellitus, a history of isotretinoin use during the last year, pregnancy or breastfeeding, consumption of any painkillers other than the prescribed ones, and experiencing any complication during surgery.

Demographic data, including age, sex, history of systemic or ocular diseases, previous history of eye surgery, and medication history were recorded with a questionnaire.

Surgical Technique

Corneal Crosslinking The traditional Dresden protocol for epithelium-off CXL was followed for all crosslinking cases. Briefly, after patients were prepped and draped, the epithelium was removed from the central 9.0 mm of the cornea with the use of concentrated ethyl alcohol 20% for 10 seconds. The loosened epithelium was fully removed with a sponge in a circular pattern. Riboflavin in a 20% dextran solution was applied every 5 minutes for 30 minutes followed by irradiation of the area with 3 mW/cm^2 of UV light at a wavelength of 365 nm for 30 minutes by a CCL365-Vario unit (MLase AG). During irradiation, 1 drop of riboflavin was instilled in the eye every 3 minutes.

Photorefractive Keratectomy After the patients were prepped and draped in the standard ophthalmic fashion, the corneal epithelium was removed in the same manner as described for the CXL group. Photorefractive keratectomy was performed with a Technolas 217 excimer laser, model P 100 (Busch & Lomb, Inc.). Mitmycin-c 0.02% was applied according to the institute nomogram.

Postoperative Treatment, Evaluations, and Pain-Rating Scales

After CXL or PRK, a soft silicon hydrogel contact lens, (PureVision-2, Bausch & Lomb, Inc.) was placed in each eye and removed after the fifth day. Patients received levofloxacin eyedrops 5 mg/mL every 6 hours and betamethasone 1.0% eyedrops every 6 hours for the first week. Preservative-free artificial tears were prescribed every 3 hours for the first week along with diclofenac 0.1% every 6 hours for up to 2 days.

The examiner was masked to the patients' allocated groups at all timepoints. Patients in both groups were examined and compared regarding the level of pain, epithelial defect size, and surgical complications immediately after surgery, 6 hours postoperatively, and 1, 3, and 7 days after the surgical procedure. Any type of corneal infection, ulcers, or immunologic reactions of the conjunctiva were also recorded during the study period.

The epithelial defect diameter was measured with calipers at the slitlamp after staining the cornea with fluorescein. The area was calculated in mm^2 $\{\pi[(a + b)/4]^2\}$, where a is the maximum diameter and b is the minimum diameter.[15]

Postoperative pain was evaluated with 3 different rating scales immediately after surgery as well as 6 hours and 1, 3, and 7 days after surgery. The visual analogue scale (VAS)[16] scores from 0 to 10; in this scale, the patient is asked to rate his or her pain by choosing a number that best describes the pain. The verbal rating scale (VRS)[A] scores from 0 to 4; in this scale the patient is asked about how the pain seems to him or her qualitatively, and the examiner gives a numeric value to the patient's description, so that "no pain" is marked as 0, "mild pain" as 1, "moderate pain" as 2, "severe pain" as 3, and "unbearable" as 4. Wong-Baker FACES[B] pain scale scores from 0 to 10 (even numbers only) while the examiner assesses the patient's pain according to his or her facial expression.

Pain Evaluation

Pain-rating scales including VRS, VAS, and FACES were evaluated and analyzed by using generalized estimating equations. The timepoints for recording the level of patients' pain were immediately after surgery, 6 hours after surgery, and on the first, third, and seventh postoperative days.

Statistical Analyses

The collected data were analyzed using SPSS software (version 16, SPSS, Inc.). Generalized linear model, generalized estimating equations, and repeated measures tests were used wherever appropriate. A P value less than 0.05 was considered statistically significant.

RESULTS

The study comprised 68 patients (34 patients in each group). The mean ages of the patients in the PRK group and CXL group were 29 years $\pm$ 1.19 (SD) and 28 $\pm$ 0.73 years, respectively ($P > .05$). No intraoperative or postoperative adverse events occurred and all patients completed the 1-week follow-up.

Epithelial Defect Area Comparison

The size of the epithelial defect did not differ significantly between the PRK and CXL groups at 6 hours