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Comparison of ocular discomfort after three different epithelial debridement techniques for corneal collagen cross-linking in keratoconus treatment

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Hosamadden Alkayid, Leyla Asena, Aslihan Yüce, Meriç Yavuz Çolak and Dilek Dursun Altınörs

Abstract

Purpose: To compare the severity and duration of ocular discomfort after three different epithelial debridement techniques for corneal collagen cross-linking in the treatment of keratoconus.

Methods: Fifty-five patients (65 eyes) known to have keratoconus were enrolled in this retrospective study. The eyes were divided into three groups based on the technique used for epithelial debridement for corneal collagen cross-linking procedure; excimer laser transepithelial phototherapeutic keratectomy was used in group 1 (18 eyes), alcohol-assisted epithelial removal was used in group 2 (27 eyes), and mechanical epithelial debridement was used in group 3 (20 eyes). Preoperative and postoperative (third month) best-corrected visual acuity (BCVA) using Snellen chart, objective refraction, and keratometry results were recorded. The results of the questionnaire obtained from the patient's medical records were reviewed regarding their subjective evaluation of postoperative symptoms including foreign body sensation, tearing, photophobia, and burning at the end of the first postoperative week. Paired-samples *t* test was used to compare preoperative and postoperative clinical findings. One-way analysis of variance (ANOVA) was used to analyze the differences between three independent groups.

Results: BCVA improved from 0.51 ± 0.27 to 0.58 ± 0.21 ($p = 0.05$). Objective mean spherical and cylindrical refraction decreased from -5.08 ± 2.78D to -4.46 ± 2.91D ($p = 0.22$) and from -3.45 ± 2.73D to -3.03 ± 1.97D ($p = 0.25$). Mean maximum keratometry reading (K_{max}) decreased from 57.63 ± 4.73D to 56.13 ± 4.47D ($p = 0.001$). The mean score for foreign body sensation was the highest in group 3 (4.50 ± 0.53) and the lowest in group 1 (2.10 ± 1.85) ($p = 0.01$). The mean scores for tearing, photophobia, and burning sensation were comparable in three groups ($p = 0.84$, $p = 0.13$, and $p = 0.61$, respectively). The duration of photophobia was the shortest in group 1 (1.50 ± 2.37 days), followed by group 3 (2.00 ± 1.31 days) and group 2 (4.00 ± 1.83 days) ($p = 0.04$).

Conclusions: The severity and duration of adverse subjective symptoms during the first postoperative week after corneal collagen cross-linking appear to be milder with epithelial debridement using excimer laser transepithelial technique compared with -assisted debridement and mechanical debridement.

Keywords: corneal collagen cross-linking, epithelial removal, excimer laser, pain

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Correspondence to:
Hosamadden Alkayid
Jordanian Royal Medical Services, King Hussein Medical Center, Amman, Jordan.

Current address:
Department of Ophthalmology, Faculty of Medicine, Başkent University, Ankara, Turkey
dr.husamahmad@yahoo.com

Leyla Asena
Aslihan Yüce
Meriç Yavuz Çolak
Dilek Dursun Altınörs
Department of Ophthalmology, Faculty of Medicine, Başkent University, Ankara, Turkey

Introduction

Keratoconus (KC) is a corneal ectatic disorder associated with progressive corneal thinning and bulging.[1] Resultant irregular astigmatism and stromal scarring often have a significant negative impact on quality of life.[1–5] Corneal collagen cross-linking (CXL) is considered a first-line treatment that can slow down or even stop KC progression.[4] It has been shown that CXL has beneficial effects on corneal optics and vision in patients with progressive KC, with few reported complications.[2,3] CXL enhances corneal rigidity by increasing the degree of covalent bonding between and within the molecules of collagen fibrils and the proteoglycans using riboflavin and ultraviolet-A (UVA) light.[1–6]

Currently, the most widely accepted protocol for CXL includes de-epithelialization of the cornea before the administration of riboflavin to increase its penetration throughout the corneal stroma and thus achieve a high level of UVA absorption.[3–6] In the procedure described by Wollensak and colleagues,[7] epithelial removal by mechanical scraping is recommended. Alcohol-assisted mechanical epithelial debridement is another commonly used technique both in CXL and in photorefractive keratectomy (PRK)-type refractive surgical procedures.[8,9] Concentrations of ethanol ranging from 10% to 30% are widely used to remove the corneal epithelium before PRK. It has been suggested that a faster and more circumscribed epithelial removal is achieved when using alcohol rather than a scalpel blade.[9]

In a new approach, excimer laser transepithelial phototherapeutic keratectomy protocol, laser ablation is used to remove the epithelium and anterior irregular corneal stroma before CXL is performed.[3,10] It has been suggested that epithelial removal using transepithelial phototherapeutic keratectomy (t-PTK) before CXL results in better visual and refractive outcomes than mechanical epithelial removal in KC patients.[10–14] In our study, the severity and duration of ocular discomfort were evaluated after performing CXL with mechanical, alcohol-assisted, or t-PTK epithelial removal in patients with progressive KC. The effect of the epithelial debridement technique during CXL on severity of postoperative ocular discomfort was assessed.

Materials and methods

This retrospective comparative study was performed in the Ophthalmology Department, Cornea and Refractive Surgery Unit of Başkent University Faculty of Medicine, Ankara, Turkey. The study was performed according to the tenets of the Helsinki Declaration and approved by the University's ethics committee (Başkent University Faculty of Medicine Clinical Research Ethics Committee; Approval ID: KA16/277). Written informed consent was obtained from all patients after they were fully informed about the purpose of the study.

In all, 65 eyes of 55 KC patients who had CXL in our clinic between April 2017 and June 2019 were included in the study. The mean age of the patients was 26 (range, 17–47) years, and the male/female ratio was 36/19. The diagnosis of KC was based on clinical signs and symptoms of KC, including irregular astigmatism, Munson sign, scissors reflex during retinoscopy, corneal thinning, Fleischer ring, Vogt striae, increased visibility of the corneal nerves, and Rizzuti sign, in addition to topographic appearance of the corneal maps obtained by a Pentacam-based corneal tomography system (WaveLight® Oculyzer™; WaveLight AG, Erlangen, Germany).[15]

Exclusion criteria included corneal thickness less than 400 μm; previous corneal surgery; current or planned pregnancy; accompanying ocular pathologies including severe allergy, recurrent corneal erosion syndrome, corneal ulcers, or scarring; current or recent use of Accutane; history of delayed epithelial healing; and nystagmus or other conditions preventing proper patient fixation. The preoperative and postoperative evaluations consisted of medical and ophthalmological history, Snellen best-corrected visual acuity (BCVA), slit-lamp evaluation, intraocular pressure (IOP) measurement, fundoscopic evaluation, and topographic analysis of the cornea by Scheimpflug imaging.[16,17]

CXL was performed after excimer laser t-PTK in 18 eyes (group 1), alcohol-assisted epithelial removal in 27 eyes (group 2), and mechanical epithelial debridement in 20 eyes (group 3). Ten patients had bilateral treatment and 45 patients had unilateral treatment. When CXL was applied to both eyes, there was at least 1-month interval between the two interventions. The technique of epithelial debridement was mechanical in the procedures performed between April 2017 and July 2017, alcohol-assisted between August 2017 and September 2018, and excimer laser t-PTK was started to be used in our department after September 2018. Preoperative and 3-month postoperative

BCVA, objective refraction, and keratometry results were recorded. The results of the questionnaire that was routinely administered by the same trained staff member to all patients undergoing CXL or refractive surgery at our unit were reviewed. The questionnaire includes subjective evaluation of postoperative symptoms of foreign body sensation, tearing, photophobia, and burning during the first postoperative week using a pain and symptom checklist. The severity of those symptoms was assessed by a scoring system ranging between 0 and 5, in which a score of 5 stands for extremely severe symptoms and a score of 0 reflects the absence of those subjective symptoms. The duration of those symptoms was recorded as well.

Paired-samples *t* test was used to compare preoperative and postoperative clinical findings. One-way analysis of variance (ANOVA) with Bonferroni post hoc test was used to determine the differences between three independent groups. Chi-square test was used to compare categorical demographic characteristics in three groups.

Surgical technique

All procedures were performed at Başkent University Faculty of Medicine, Department of Ophthalmology, by the same refractive surgeon (D.D.A.) under sterile conditions. Proparacaine hydrochloride (0.5%, Alcaine drops; Alcon Lab) was used for topical anesthesia in all study groups, before epithelial removal.

In group 1, epithelial removal was performed by excimer laser t-PTK using PTK mode of the Allegretto ex400 Wavelight excimer laser system with an 8-mm optical zone profile and 50-µm ablation depth. In group 2, the corneal epithelium was removed mechanically after applying a 20% alcohol-saturated triangular merocele sponge for 10 s and then rinsed with balanced salt solution, and in group 3, the corneal epithelium was removed mechanically using a crescent knife, at an intended 8-mm zone.

After epithelial removal, all patients were treated with CXL according to the standard protocol, described by Wollensak and colleagues.[7] Riboflavin drops were applied on the center of the cornea every 2 min for 30 min until stromal saturation was confirmed by the presence of riboflavin flare in the anterior chamber. Isotonic riboflavin (riboflavin 0.1% in dextran 20.0% T500 solution) was used. Ultraviolet-A (UVA) irradiation was accomplished using a commercially available UVA system (irradiation at 365 nm and 3 mW/cm^2 for 30 min). During treatment, riboflavin solution was applied every 2 min to ensure saturation and a balanced salt solution was applied every minute to moisten the cornea.

A silicone hydrogel bandage contact lens (Acuvue Oasys; Johnson & Johnson Vision Care) was applied at the end of the surgery until full re-epithelialization of the cornea. Postoperative treatment included moxifloxacin eye drops 4 times daily for 1 week, dexamethasone eye drops 4 times daily on a tapering schedule for 1 month, and artificial tears 4 times daily for 6 months. Postoperative oral analgesic medication was not prescribed. The contact lens was removed at the fourth to sixth postoperative day in all groups.

Results

Demographic characteristics including age and sex were comparable in all groups with no statistically significant differences (Table 1).

The mean Snellen BCVA increased from 0.51 ± 0.27 to 0.58 ± 0.21 ($p = 0.05$). Objective mean spherical and cylindrical refraction decreased from -5.08 ± 2.78D to -4.46 ± 2.91D ($p = 0.22$) and from -3.45 ± 2.73D to -3.03 ± 1.97D ($p = 0.25$) on the postoperative third month. Mean maximum keratometry reading (K_{max}) decreased from 57.63 ± 4.73D to 56.13 ± 4.47D ($p = 0.001$). Preoperative and postoperative visual acuity, and refractive and keratometric values in the study population are shown in Table 2.

The mean score for foreign body sensation was the highest in group 3 (4.50 ± 0.53) followed by group 2 (2.71 ± 1.97) and then group 1 (2.10 ± 1.85) ($p = 0.01$). The mean scores for tearing and photophobia were the lowest in group 1, and similar scores were observed in groups 2 and 3, although these differences were not statistically significant ($p = 0.84$ and $p = 0.13$ respectively). The mean score for burning sensation was the highest in group 3 with similar values in groups 1 and 2, although not statistically significant as well ($p = 0.61$). Comparison of the mean scores for each subjective symptom in three groups is shown in Table 3.

The duration of photophobia was the shortest in group 1 (1.50 ± 2.37 days), followed by group 3

Table 1. Comparison of the demographic characteristics of the participants in three different study groups.

	Group 1	Group 2	Group 3	Total	P value
Mean age	28.9 ± 8.1	24.9 ± 7.0	26.2 ± 4.6	26.5 ± 6.8	0.35[a]
Sex					
Male	12 (33%)	11 (31%)	13 (36%)	36	0.42[b]
Female	5 (26%)	8 (42%)	6 (32%)	19	0.44[b]

Results are described as 'mean ± standard deviation' or 'number of participants (%)'.
[a]One-way analysis of variance.
[b]Chi-square test.

Table 2. Mean preoperative and postoperative visual acuity, and refractive and keratometric values in the study population.

	Preoperative	Postoperative third month	*p* value[a]
Snellen BCVA	0.51 ± 0.27	0.58 ± 0.21	0.05
Spheric objective refraction.	−5.08 ± 2.78D	−4.46 ± 2.91D	0.22
Cylindric objective refraction	−3.45 ± 2.73D	−3.03 ± 1.97D	0.25
Maximum keratometry (K_{max})	57.63 ± 4.73D	56.13 ± 4.47D	0.001
Flat keratometry (K_1)	46.8 ± 3.2D	45.8 ± 2.8D	< 0.001
Steep keratometry (K_2)	50.7 ± 3.8D	49.6 ± 3.6D	0.001

BCVA, best-corrected visual acuity; D, diopter.
Results are described as 'mean ± standard deviation'.
[a]Paired-samples *t* test.

(2.00 ± 1.31 days) and then group 2 (4.00 ± 1.83 days) ($p = 0.04$). The duration of tearing and burning sensation lasted the longest in group 2 ($p = 0.58$ and $p = 0.58$, respectively) and the duration of foreign body sensation and burning was the shortest in group 1 ($p = 0.86$ and $p = 0.58$, respectively); however, these differences were not statistically significant. Comparison of the duration of each subjective symptom in three groups is shown in Table 4.

No complications were observed in any of the study groups, including infective keratitis, herpetic keratitis reactivation, intraocular inflammation, or IOP elevation. A typical corneal haze was observed in all patients; however, none of the patients experienced any visual loss.

As a result, foreign body sensation was the most severe in patients who underwent mechanical epithelial debridement and the mildest with excimer laser t-PTK epithelial removal in the first week after CXL. Photophobia appeared to be shortest in duration with excimer laser t-PTK epithelial removal and longest with alcohol-assisted epithelial debridement.

Discussion

Studies have suggested that CXL should be performed following debridement of the central corneal epithelium to enable riboflavin to efficiently distribute through the corneal stroma. However, epithelial debridement may cause significant pain and visual disturbance in the immediate postoperative period.[6] The possible complications and ocular discomfort related to corneal epithelial removal have led to conduction of studies about corneal cross-linking without epithelial removal (Epi-on CXL),[4,17–19] which showed much less efficacy compared with Epi-on CXL.[18] Therefore, it was not recommended to substitute Epi-off

Table 3. Comparison of the mean scores for each subjective symptom in three groups.

Epithelial removal technique	Group 1 (*n*: 18) (excimer laser t-PTK)	Group 2 (*n*: 27) (alcohol-assisted)	Group 3 (*n*: 20) (mechanical)	*p* value[a]
Foreign body sensation score	2.10 ± 1.85 (0–5)	2.71 ± 1.97 (0–5)	4.50 ± 0.53 (4–5)	0.01[b]
Tearing score	2.30 ± 2.05 (0–5)	2.70 ± 1.71 (0–4)	2.87 ± 2.47 (0–5)	0.84
Photophobia score	1.90 ± 2.46 (0–5)	3.85 ± 1.34 (2–5)	3.12 ± 1.55 (0–5)	0.13
Burning sensation score	2.30 ± 1.41 (0–4)	2.28 ± 1.88 (0–5)	3.00 ± 1.69 (0–5)	0.61

t-PTK, transepithelial phototherapeutic keratectomy.
Results are described as 'mean ± standard deviation (range)'.
[a]One-way analysis of variance.
[b]Statistically significant.

Table 4. Comparison of the duration of each subjective symptom in three groups.

Epithelial removal technique	Group 1 (*n*: 18) (excimer laser t-PTK)	Group 2 (*n*: 27) (alcohol-assisted)	Group 3 (*n*: 20) (mechanical)	*p* value[a]
Duration of foreign body sensation (days)	1.90 ± 2.33 (0–7)	2.29 ± 2.42 (0–7)	2.50 ± 2.26 (1–7)	0.86
Duration of tearing (days)	1.0 ± 0.82 (0–2)	1.57 ± 0.98 (0–3)	0.80 ± 1.03 (0–3)	0.58
Duration of photophobia (days)	1.50 ± 2.37 (0–7)	4.00 ± 1.83 (2–7)	2.00 ± 1.31 (0–4)	0.04[b]
Duration of burning sensation (days)	1.50 ± 1.65 (0–5)	2.43 ± 2.44 (0–7)	1.75 ± 1.28 (0–4)	0.58

t-PTK, transepithelial phototherapeutic keratectomy.
Results are described as 'mean ± standard deviation (range)'.
[a]One-way analysis of variance.
[b]Statistically significant.

CXL with Epi-on CXL for the treatment of progressive KC. However, the patient's discomfort after surgery is strongly related to the degree and speed of corneal epithelium healing. A list of complications was reported after debridement of corneal epithelium, which included delayed epithelial healing, persistent epithelial defects, secondary infection, contact lens–related infection, haze, and opacities.[20] Postoperative pain related to epithelial removal in CXL is still an important issue which needs special consideration.

Our study documented and compared the short-term postoperative subjective adverse symptoms experienced by the patients during the healing process of the corneal epithelium after corneal CXL. Our aim was to determine the most comfortable technique to be used for epithelial removal during the CXL procedure. The study showed that the severity and duration of subjective symptoms during the first postoperative week after CXL appear to be the mildest with epithelial debridement when performed by excimer laser t-PTK compared with alcohol-assisted debridement and mechanical debridement.

Although pain is one of the most important postoperative adverse symptoms of CXL, the experience of ophthalmic pain is subjective and complicated. In a study aiming to develop a categorical ophthalmic pain severity scale, a five-category scale was found to be useful with category labels as 'extreme', 'severe', 'moderate', 'mild', and 'none' for assessing the severity of ophthalmic sensations.[14] This study highlighted the importance of giving the patients the opportunity to

describe other attributes or effects of the pain sensation including 'discomfort' or 'light sensitivity'. Foreign body sensation, tearing, photophobia, and burning sensation are other symptoms related to ocular discomfort that have been described by most patients in previous studies.[9–11,21] Therefore, a similar five-category scale scoring system was used in this study, which included the above-mentioned, commonly used attributes for the description of ocular discomfort.

Epithelial removal during CXL can be performed with standard mechanical debridement (with or without the use of alcohol) or with recently used excimer laser t-PTK. The excimer laser was first used in conjunction with CXL treatment in KC patients in 2007 in the Athens protocol (combined topography-guided photorefractive keratectomy and CXL), which reported good safety records and effective results.[22] In the case of CXL with t-PTK epithelial debridement technique at an ablation depth of 50 µm, epithelium is removed in addition to a small amount of anterior stromal tissue on the central steep thin cornea, which causes some smoothening of the anterior stromal surface.[10] t-PTK epithelial removal during CXL has been shown to result in better visual and refractive outcomes in comparison with mechanical epithelial debridement.[10]

Alcohol-assisted epithelial debridement is another option to remove the corneal epithelium. In a previous study comparing alcohol with mechanical debridement in patients who underwent bilateral PRK, results showed a trend toward a quicker visual rehabilitation in the alcohol-treated patients along with equivalent safety and efficacy.[23] In another similar study, a faster and more circumscribed epithelial removal was achieved when using alcohol rather than a scalpel blade.[9] There was also a trend toward more haze in the mechanically scraped patients over the course of the same study. To the best of our knowledge, this is the first study to compare ocular discomfort after CXL with three different epithelial debridement techniques.

Foreign body sensation was the most severe with mechanical followed by alcohol-assisted and excimer laser t-PTK epithelial removal, respectively. Severity of tearing, photophobia, and burning sensation were all highest with mechanical debridement technique and lowest with excimer laser t-PTK epithelial removal, although these differences were not statistically significant. The duration of photophobia was the shortest with excimer laser t-PTK epithelial removal and the longest with alcohol-assisted epithelial debridement. Although the duration of foreign body sensation and burning was also the shortest in the excimer laser t-PTK epithelial removal group, these differences were not statistically significant.

The most important limitation of our study was the sample size which was relatively small. As perception of ocular discomfort is subjective and highly heterogeneous, including a larger number of patients might lead to more reliable results. However, the three groups in our study had similar demographic characteristics including age and sex. Furthermore, all patients underwent an interview-based questionnaire immediately at the first postoperative week when their memory of ocular sensations was still fresh. These are important factors to decrease bias in our study.

As a result, the severity and duration of subjective symptoms during the first postoperative week after CXL including foreign body sensation, tearing, photophobia, and burning appeared to be the mildest with epithelium removal by excimer laser t-PTK. Therefore, removal of corneal epithelium using transepithelial PTK during CXL could be a good choice to achieve better postoperative patient comfort and decrease the severity of foreign body sensation and duration of photophobia.

Conflict of interest statement

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ORCID iD

Hosamadden Alkayid https://orcid.org/0000-0002-8052-9400

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