Original Article

Corneal Collagen Cross-Linking Using Epithelium Disruptor Instrument in Progressive Keratoconus

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Abstract

Purpose: To compare the effects of accelerated corneal collagen cross-linking (CXL) in progressive keratoconus (KCN) patients via epithelium removal and transepithelial techniques, using Daya Disruptor (Duckworth and Kent, Hertfordshire, UK).

Methods: This study is a double-blinded, randomized clinical trial. Patients with documented bilateral progressive KCN were randomized into two groups: one eye underwent epithelium removal (Group 1), and the fellow eye underwent epithelium disruption (Group 2). The primary outcomes were best corrected visual acuity (BCVA) and uncorrected visual acuity (UCVA), Scheimpflug-extracted keratometric indices, and anterior segment-optical coherence tomography-derived epithelial thickness profiles. These parameters were evaluated before and 12 months after CXL.

Results: Sixty-four eyes from 34 patients with progressive KCN (34 eyes in the epithelium-removal group and 30 eyes in the epithelium-disruption group) were included. The mean ± standard deviation (SD) of age was 23.4 ± 3.8 years in the epithelium-removal group and 23.2 ± 3.5 years in the epithelium-disruption group. The mean ± SD of the preoperative spherical equivalent (SE), front maximum keratometry (K-max), back K-max, thickness of thinnest point, and corneal apex thickness were − 2.9 ± 3.0 diopter (D) and − 3.7 ± 3.1 D ($P = 0.183$), 53.8 ± 5.15 D and 54.4 ± 5.53 D ($P = 0.653$), −6.63 ± 2.40 D and − 6.68 ± 2.48 D ($P = 0.131$), 459.2 ± 37.4 μm and 460.8 ± 32.7 μm ($P = 0.708$), 470.5 ± 37.7 μm and 469.7 ± 33.1 μm ($P = 0.679$), and 55.4 ± 4.97 μm and 54.6 ± 7.16 μm ($P = 0.767$) in the epithelium-removal and epithelium-disruption groups, respectively. The mean ± SD changes of the UCVA and BCVA 12 months after CXL were − 0.1 ± 0.11 and − 0.02 ± 0.18 and − 0.04 ± 0.12 and − 0.02 ± 0.14 in the epithelium-removal and epithelium-disruption groups, respectively. No statistically significant improvement was observed in the UCVA and BCVA between the two groups ($P = 0.868$ and $P = 0.937$, respectively). The mean ± SD changes of the SE, superior epithelial thickness, corneal apex thickness, and thickness of thinnest point 12 months after CXL were − 0.21 ± 1.1 D and + 0.32 ± 1.6 D ($P = 0.0001$), −0.08 ± 0.26 μm and + 0.03 ± 0.33 μm ($P = 0.028$), −23 ± 11 μm and − 2 ± 6 μm ($P = 0.0001$), and − 25 ± 8 μm and − 3 ± 7 μm ($P = 0.0001$) in the epithelium-removal and epithelium-disruption groups, respectively.

Conclusions: This study showed that the epithelium-disruption CXL using Daya has a similar potential for halting KCN progression as the epithelium-removal CXL. However, regarding the 12-month changes, the epithelium-disruption CXL is superior to the epithelium-removal CXL in the SE and corneal pachymetry.

Keywords: Collagen cross-linking, Cornea, Epithelium-disruption, Epithelium-removal, Keratoconus

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Introduction

Keratoconus (KCN) is a corneal non-inflammatory progressive cone-like ectasia, which is bilateral 90% of the time.[1] The KCN prevalence was 2.5% in the Tehran Eye Study.[2] KCN has a profound impact on the subjective quality of vision and life,

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especially in psychological aspects that might be overlooked by health-care providers.[3] Corneal collagen cross-linking (CXL) as a treatment that focuses on the underlying pathophysiology of the disease uses a combination of riboflavin (Vitamin B2) and ultraviolet-A (UV-A) light to strengthen the corneal tissue through photosensitization and chemical cross-linking.[4,5] Postoperative pain and complications resulting from epithelial debridement in the standard CXL procedure led to CXL without epithelial removal, known as transepithelial CXL.[6] Since the introduction of Daya epithelial disruptor by Dr. Sheraz Daya, which is a kind of transepithelial CXL, this procedure was evaluated in some previous studies.[7,8] In an Italian study on 28 patients, this procedure was reported to be safe and effective in KCN stabilization, in addition to improvement in topographic and refractive outcomes and less corneal discomfort in the medium term.[7] In another study on 128 eyes, maximum keratometry (K-max) stabilization and best corrected visual acuity (BCVA) improvement were reported within 1-year follow-up.[8]

Due to the insufficient evidence of corneal epithelial parameters in similar studies and the need for evaluation of the effectiveness of this new method in halting the progression of KCN, we designed a study to further evaluate the effect of these methods on the mentioned primary outcomes.

Methods

This double-blinded, randomized study was designed as a fellow eye-controlled trial. Its protocol was approved by the local ethics committee. The study was performed under the Declaration of Helsinki, and written informed consent was obtained from all patients. The randomized controlled trial (RCT) was registered at the Iranian Registry of Clinical Trials (No. # IRCT2016112231028N1). The study was performed at Khalili Hospital, Shiraz, Iran.

Patients satisfying Rabinowitz criteria of KCN in both eyes were included in the study. Inclusion criteria were age ≥ 18 years, clear central cornea, and a documented progression of KCN. KCN progression was defined as an increase of at least 1 diopter (D) in K-max and a reduction of at least one line in the BCVA within the last 12 months. We used the mean of three repeated measurements to increase the specificity for KCN progression identification and false-positive rate reduction. Exclusion criteria were a history of previous ocular surgery, pregnancy, lactation, corneal thickness < 400 μm, K-max > 61 D, previous ocular herpetic infection, concurrent keratitis, severe corneal opacity, poor epithelial healing, autoimmune diseases, atopy, ocular surface disorders such as dry eye, and a habit of eye rubbing.

Patients who fulfilled the criteria were enrolled in the study after signing the written informed consent. Full ocular examination was done. Uncorrected visual acuity (UCVA), BCVA, and intraocular pressure (IOP) by Topcon CT-1® non-contact tonometer (Topcon Medical Systems, Inc., Oakland, USA) were documented preoperatively and 12 months postoperatively. Scheimpflug imaging by Pentacam® HR (Oculus, Lynwood, WA, USA), anterior segment-optical coherence tomography (AS-OCT) by RTVue-100® (Optovue Inc., Fremont, Calif., USA), and automated non-contact specular microscopy by Topcon SP-3000P (Topcon Corporation, Tokyo, Japan) were performed preoperatively and 12 months postoperatively. Spectral-domain OCT was used to assess corneal epithelial thickness (minimum, maximum, superior, and inferior thickness). Specular microscopy was used to assess endothelial cell count (ECC) and coefficient of variation (CV) of endothelial cell size.

Eligible patients were randomized using stratified randomization. Randomization was done both for the first eye to be operated on and the surgical methods. In each patient, the interval period between the operation of the first eye (with the epithelium-removal CXL) and the fellow eye (with the epithelium-disruption CXL) was at least 2 weeks. Ocular imaging was performed by the same experienced ophthalmic technician preoperatively and 12 months postoperatively.

In all cases, pilocarpine 2% (Glaupin®, Sina Darou, Tehran, Iran) eye drop was applied an hour before the surgery to ensure miosis during the procedure. Tetracaine 0.5% (Anestocaine®, Sina Darou, Tehran, Iran) eye drop was also applied just before the surgery to provide topical anesthesia. In the eyes treated by epithelium-removal CXL method, corneal epithelium was removed completely by FUKASAKU Hockey Knife (Millennium Surgical Corp, Pennsylvania, USA), and then standard solution of preservative and dextran-free riboflavin 0.1% (Sina Darou, Tehran, Iran), suggested by Stojanovic *et al*.,[9] with intervals of 3 min, was distilled into the eye for 30 min. Then, distillation continued for 10 min with UV-A (365 nm) irradiation with a power of 9 mW/cm^2 at 5 cm from the eye, with a spot size of 7 mm, using CCL-365-Vario (Mlase AG, Germering, Germany). Finally, after irrigation with 30 ml of balanced salt solution, a bandage contact lens (BCL) (CIBA Vision, Duluth, GA, USA) was fitted over the eye. In the eyes treated by epithelium-disruption CXL (Daya CXL) method, corneal epithelium was disrupted by Daya epithelium disruptor (Duckworth and Kent Ltd, Hertfordshire, UK), and the rest of the procedure was performed similarly to the epithelium-removal method. The Daya Disruptor creates tiny pores in the epithelium through which the riboflavin can pass into the corneal stroma. It has 40 fine sharp points radially spaced, a 45° angled shaft, and a round handle with a length of 125 mm. The procedures were performed by the same surgeon. It should be mentioned that after saturation with riboflavin, the corneas in both groups were evaluated by a surgical microscope to ensure the penetration of the riboflavin to the mid-stroma of the cornea.

Patients were instructed to use their drops 2 h after being discharged. The prescribed medications were preservative-free artificial tear q 2 h (Artipic® 0.32%, Iranian Parenteral and Pharmaceutical Co., Tehran, Iran), levofloxacin 0.5% eye drop (LEVOFLOXID®, Tekaje Co, Tehran, Iran) q 4 h,

and betamethasone eye drop (Betasonate®, Sina Darou, Tehran, Iran) q 6 h. Acetaminophen 320-mg tablets were also prescribed for pain as needed. The patients were visited by the surgeon on the 1st day after the surgery and the following days until the healing of corneal epithelial defect (CED). After the clinical healing of CED (re-epithelialization confirmed by fluorescein staining), BCL was removed. Topical levofloxacin was discontinued after BCL removal. Betamethasone eye drop was continued for a month. The patients were instructed to use the artificial tear for at least 3 months. Pain and ocular discomfort were evaluated during each visit before BCL removal by analog pain scale. Its reliability and validity were noted by Hawker *et al*.[10] The patients were visited on the 1st and 3rd weeks for any complications. Follow-up visits were done at least 12 months after the second procedure, including slit-lamp biomicroscopy, IOP measurement, UCVA, objective refraction refined by subjective refraction, BCVA, Pentacam® imaging, AS-OCT, and specular microscopy.

Statistical analysis

The sample size was calculated with the following assumptions: statistical power of 80%, confidence interval of 95%, and effect size of 0.8. A sample size of thirty eyes per group was calculated. Based on a 10% dropout rate, a final sample size of 34 patients was planned.

Qualitative data were described in number (percent) and quantitative variables were expressed as the mean values ± standard deviation (SD). The normality of the data was checked by the Kolmogorov–Smirnov test. Before–after data were analyzed using paired-samples *t*-test or Wilcoxon test. To compare the results of the two surgeries, either Student's *t*-test or Mann–Whitney U-test was used. For bivariate correlations, Pearson's correlation or Spearman's correlation was utilized. We did an intention-to-treat analysis to solve any non-compliance and dropout after randomization. $P < 0.05$ was considered statistically significant.

Results

Thirty-four patients were included in the study. Thirty-four eyes of 34 patients underwent the epithelium-removal CXL procedure, and 30 eyes underwent the Daya CXL procedure. Four patients postponed the operation in the fellow eye due to some personal problems; therefore, the data for 4 eyes in the Daya CXL group were missing. The mean ± SD follow-up duration was 13.5 ± 2.1 months after the second eye procedure.

The demographic characteristics of the patients are shown in Table 1. The baseline preoperative characteristics in the two groups are summarized in Table 2.

The differences in the mean ± SD of the postoperative UCVA (0.4 ± 0.3 and 0.43 ± 0.32 logMAR in the epithelium-removal and Daya CXL groups, respectively) and BCVA (0.19 ± 0.1 and 0.15 ± 0.17 logMAR in the epithelium-removal and Daya CXL groups, respectively) were not statistically significant ($P > 0.05$) between the two groups [Table 3]. The mean ± SD changes in the UCVA and BCVA were − 0.1 ± 0.11 and − 0.02 ± 0.18 ($P = 0.868$) and − 0.04 ± 0.12 and − 0.02 ± 0.14 ($P = 0.937$) in the epithelium-removal and Daya CXL groups, respectively [Table 4]. No statistically significant difference was observed in the UCVA and BCVA between the two groups.

Table 1: Demographic characteristics of the patients

Parameter	Epithelium-removal CXL group ($n=34$)	Daya CXL group ($n=30$)
Age (year)	23.4±3.8	23.2±3.5
Male, *n* (%)	10 (31.3)	9 (29)
Female, *n* (%)	22 (68.8)	22 (71)

CXL: Corneal collagen cross-linking

Spherical equivalent (SE) and keratometric indices including front mean keratometry (mean K), front K-max, and back K-max were matched between the two groups. The mean ± SD changes of the SE (−0.21 ± 1.1 and + 0.32 ± 1.6 D [$P = 0.0001$] in the epithelium-removal and Daya CXL groups, respectively) were statistically significant after the operation and between the two groups [Table 4]. The mean ± SD changes of the front K-max (−0.6 ± 1.8 D and −0.7 ± 1.5 D [$P = 0.372$] in the epithelium-removal and Daya CXL groups, respectively), front mean K (−0.1 ± 1.3 D and −0.1 ± 1.6 D [$P = 0.259$] in the epithelium-removal and Daya CXL groups, respectively), and back K-max (+0.12 ± 1.1 D and + 0.13 ± 1.3 D [$P = 0.109$] in the epithelium-removal and Daya CXL groups, respectively) were not statistically significantly different between the two groups [Table 4].

The apical corneal pachymetry decreased statistically significantly after the procedure (−23 ± 11 µm and −2 ± 6 µm [$P = 0.0001$] in the epithelium-removal and Daya CXL groups, respectively), which was significantly different between the two groups [Tables 2 and 3]. In addition, the thinnest corneal pachymetry decreased statistically significantly after the procedure (−25 ± 8 µm and −2 ± 7 µm [$P = 0.0001$] in the epithelium-removal and Daya CXL groups, respectively). It should be noted that the decrease of corneal thickness did not restore after 1 year of follow-up.

Before treatment, the superior epithelial thickness (55.9 ± 6.38 µm and 55.8 ± 4.01 µm [$P = 0.694$] in the epithelium-removal and Daya CXL groups, respectively) was slightly thicker than inferior epithelial thickness (55.4 ± 4.97 µm and 54.6 ± 7.16 µm [$P = 0.767$] in the epithelium-removal and epithelial-disruption groups, respectively) in both groups [Table 2], but after the CXL, the inferior epithelial thickness (55 ± 3.5 µm and 56.7 ± 4.3 µm [$P = 0.363$] in the epithelium-removal and Daya CXL groups, respectively) was slightly thicker than the superior epithelial thickness (53.9 ± 3.4 µm and 56.1 ± 4.3 µm [$P = 0.028$] in the epithelium-removal and Daya CXL groups, respectively) in both groups [Table 3]. The changes of the superior epithelial thickness were statistically

Table 2: Baseline preoperative characteristics in the two groups

Parameter	Epithelium-removal CXL group ($n=34$)	Daya CXL group ($n=30$)	*P*
UCVA (logMAR)	0.55±0.34	0.50±0.37	0.502
BCVA (logMAR)	0.20±0.20	0.19±0.23	0.695
SE (D)	−2.9±3.0	−3.7±3.1	0.183
Front mean K (D)	45.7±3.28	46.5±2.94	0.32
Front K-max (D)	53.8±5.15	54.4±5.53	0.653
Back K-max (D)	−6.63±2.40	−6.68±2.48	0.131
Apex pachymetry (μm)	470.5±37.7	469.7±33.1	0.679
Thinnest pachymetry (μm)	459.2±37.4	460.8±32.7	0.708
Min Epi* (μm)	44.7±5.18	44.8±4.95	0.945
Max Epi* (μm)	63.7±7.1	63.2±5.1	0.858
S* (μm)	55.9±6.38	55.8±4.01	0.694
I* (μm)	55.4±4.97	54.6±7.16	0.767

*Extracted from AS-OCT. CXL: Corneal collagen cross-linking, UCVA: Uncorrected visual acuity, BCVA: Best corrected visual acuity, SE: Spherical equivalent, D: Diopter, Mean K: Mean keratometry, K-max: Maximum keratometry, Min Epi: Minimum epithelial thickness, Max Epi: Maximum epithelial thickness, S: Superior epithelial thickness, I: Inferior epithelial thickness, AS-OCT: Anterior segment-optical coherence tomography

Table 3: The mean±standard deviation of parameters 12 months after the procedure in the two groups

Parameter	Epithelium-removal CXL group ($n=34$)	Daya CXL group ($n=30$)	*P**
UCVA (logMAR)	0.4±0.3	0.43±0.32	0.868
BCVA (logMAR)	0.19±0.1	0.15±0.17	0.937
SE (D)	−3.2±2.8	−3.3±2.7	0.0001**
Front mean K (D)	45.9±6.3	46.9±3.1	0.259
Front K-max (D)	53.2±7.7	53.9±5.1	0.372
Back K-max (D)	−7.4±1.2	−7.1±0.6	0.109
Apex pachymetry (μm)	440±46	466±39	0.0001**
Thinnest pachymetry (μm)	428±46	455.2±39	0.0001**
Min Epi (μm)	45.6±4.7	46.2±3.9	0.483
Max Epi (μm)	61.7±4.7	64.3±5.9	0.081
S (μm)	53.9±3.4	56.1±4.3	0.028
I (μm)	55±3.5	56.7±4.3	0.363
BCL removal (days)	4.5±1.3	3.1±1.1	<0.0001
Postoperative pain (analog pain score)	4.4±2.5	2.4±1.8	0.001**

*Change of the variables before and after treatment was compared between the two groups, **Indicates for statistically significant *P* value, ($P<0.05$). CXL: Corneal collagen cross-linking, UCVA: Uncorrected visual acuity, BCVA: Best corrected visual acuity, SE: Spherical equivalent, D: Diopter, Mean K: Mean keratometry, K-max: Maximum keratometry, Min Epi: Minimum epithelial thickness, Max Epi: Maximum epithelial thickness, S: Superior epithelial thickness, I: Inferior epithelial thickness, BCL: Bandage contact lens

significant between the two groups (−0.08 ± 0.26 μm and +0.03 ± 0.33 μm [$P = 0.028$] in the epithelium-removal and Daya CXL groups, respectively) [Table 3]. Furthermore, the global epithelial thickness changes were statistically different between the two groups (−1.5 ± 0.31 μm and +1.1 ± 0.26 μm for epithelium-removal and Daya CXL groups, respectively). The differences between the thinnest and thickest points of the epithelium before (19 ± 3.1 μm and 18.4 ± 2.9 μm [$P > 0.05$] in the epithelium-removal and Daya CXL groups, respectively) and after treatment (16.1 ± 2.9 μm and 18.1 ± 3.1 μm [$P > 0.05$] in the epithelium-removal and Daya CXL groups, respectively) were not statistically significantly different between the two groups. However, the changes of differences between the thinnest and thickest points of the epithelium were statistically significant after the CXL procedures in both groups (−3.1 ± 1.5 μm and −0.3 ± 1.4 μm [$P < 0.05$] in the epithelium-removal and Daya CXL groups, respectively).

ECC and CV of endothelial cell size matched preoperatively between the two groups. Before–after analysis as shown in Table 5 revealed no statistically significant changes ($P = 0.127$ and 0.804, for ECC and CV, respectively). The time of resolution of epithelial defect, which was shown as of BCL removal and postoperative pain, is shown in Table 3. It was statistically and clinically less for the Daya CXL group.

Discussion

The current study is a double-blinded (optometrist and the patients), fellow eye-controlled RCT designed to compare the effectiveness of epithelium-removal CXL and Daya CXL in 12-month follow-up duration.

Table 4: The mean±standard deviation changes of parameters after the procedures in the two groups

Parameter	Epithelium-removal CXL group (n=34)	Daya CXL group (n=30)	P
UCVA (logMAR)	−0.1±0.11	−0.02±0.18	0.868
BCVA (logMAR)	−0.04±0.12	−0.02±0.14	0.937
SE (D)	−0.21±1.1	+0.32±1.6	0.0001*
Front mean K (D)	−0.1±1.3	−0.1±1.6	0.259
Front K-max (D)	−0.6±1.8	−0.7±1.5	0.372
Back K-max (D)	+0.12±1.1	+0.13±1.3	0.109
Apex pachymetry (μm)	−23±11	−2±6	0.0001*
Thinnest pachymetry (μm)	−25±8	−3±7	0.0001*
Min Epi (μm)	+0.01±0.22	+0.01±0.18	0.483
Max Epi (μm)	−0.02±0.31	+0.01±0.41	0.081
S (μm)	−0.08±0.26	+0.03±0.33	0.028*
I (μm)	−0.01±0.21	+0.03±0.18	0.363

*Indicates for statistically significant P value, (P<0.05). CXL: Corneal collagen cross-linking, UCVA: Uncorrected visual acuity, BCVA: Best corrected visual acuity, SE: Spherical equivalent, D: Diopter, Mean K: Mean keratometry, K-max: Maximum keratometry, Min Epi: Minimum epithelial thickness, Max Epi: Maximum epithelial thickness, S: Superior epithelial thickness, I: Inferior epithelial thickness, BCL: Bandage contact lens

Table 5: Before/after values of endothelial cell count, coefficient of variation of endothelial cell size, and intraocular pressure

Parameter	Preoperative	Postoperative	P
ECC (cells/mm^2)	2524±717	2720±347	0.127
CV of endothelial cell size	0.3±0.11	0.28±0.07	0.804
IOP (mmHg)	11±2	10.5±2	_

ECC: Endothelial cell count, CV: Coefficient of variation, IOP: Intraocular pressure

Our data show that Daya CXL has better results not only in the SE but also in the apical and thinnest point of pachymetry. We found that both groups have similar results according to keratometric indices. Although several studies compared transepithelial CXL with the epithelium-removal CXL, there is not enough agreement over the results [Table 6]. Lesniak and Hersh compared 1- and 2-min intervals of riboflavin administration in transepithelial CXL procedure. In their study on 35 eyes, K-max was flattened by 0.9 D and BCVA improved by 0.83 Snellen line.[13] In another retrospective cohort by Çerman *et al*. with 18-month follow-up, the mean UCVA and BCVA were reported as 0.12 and −0.11, respectively. The improvement in mean UCVA and BCVA in their study was statistically significant (P < 0.001).[14] In addition, Magli *et al*. compared transepithelial CXL with epithelium-off CXL in a pediatric population and showed similar effectiveness.[15] However, Caporossi *et al*. reported improvements in BCVA at 3 and 6 months plus stabilization of keratometric indices in 12 months and worsening at 24 months.[16] Al Fayez *et al*. in an RCT on seventy eyes compared epithelium-removal CXL with transepithelial CXL in 3-year follow-up. They reported a mean reduction of 2.4 D in K-max of the epithelium-removal CXL group and no progression in KCN patients, while in the transepithelial group, K-max increased by a mean of 1.1 D, and there was KCN progression in twenty patients (55%).[17] In a systematic review and meta-analysis study, both epithelium-removal and transepithelial CXL have been proven to halt KCN progression effectively. Significant inferiority of modified CXL relative to epithelium-removal CXL at halting K-max deterioration is found in progressive KCN. However, visual acuity improvement showed similar results. They recommended transepithelial CXL for patients with a corneal thickness of <400 μm.[18] A point that was overlooked in the above review is that the epithelium disruption method was not classified as a separate category.[11,18] We believed that partial-epithelial removal methods are different from those transepithelial methods, and also Daya CXL is a kind of partial-epithelial removal method. Table 6 compares the results of the current study with the studies that utilize partial epithelial-removal methods.

Several advantages were reported for transepithelial CXL in comparison to epithelium-off CXL. These advantages include faster visual recovery, the ability to wear contact lenses sooner, as well as reduced pain.[7,8,10-12,18] Maintenance of the epithelium in the transepithelial CXL method might decrease corneal thinning during the CXL procedure. In addition, it might allow the treatment of more severe KCNs with a thin corneal thickness.[11,12,18] In our study, the safety profile for corneal endothelium, ECC, and CV showed no significant changes after both procedures. The time of BCL removal, which was the indicator of the time needed for re-epithelialization, was significantly less in the Daya CXL group in comparison to the epithelium-removal CXL group. Reported pain during the first several days was significantly lower for the epithelium-disruption CXL group in comparison to the epithelium-removal CXL group. Moreover, adverse complications, including corneal infiltration, scarring, and increased IOP due to corticosteroid eye drops, were not detected. It is necessary to clarify that a slight corneal haze that did not affect visual acuity occurred in both groups, but was unmeasurable to be reported.

Recently, epithelial thickness profiles are utilized for early detection and monitoring of the corneal ectatic disorders'

Table 6: The results of the current study and other studies that utilize partial-epithelium removal method and epithelial disruptor instruments

Study	Study design	Mean K (D)	BCVA (logMAR)	UCVA (logMAR)	CCT (μm)	Follow-up (m)	Number of patients
Rechichi *et al*.[7]	Prospective comparative case series	Δ=−3.03 Compared to baseline	Δ=−0.05 Compared to baseline	Δ=−0.25 Compared to baseline	Δ=12 Compared to baseline	12	Daya: 28
Hirji *et al*.[8]	Retrospective case series[a]	Δ=−0.3 Compared to baseline at 12 months	Δ=0.1 Compared to baseline at 12 months	Δ=0.1 Compared to baseline at 12 months	Not reported	9−12	Daya: 128
Galvis *et al*.[11]	Retrospective interventional case series	Δ=−0.1 Compared to baseline	Δ=−0.04 Compared to baseline	Not reported	Δ=1 Compared to baseline	69.6	Partial deepithelization* 80 eyes
Hashemi *et al*.[12]	Retrospective comparative study	More improvement in Conventional Δ=−0.42 *P*=0.015	More improvement in partial Δ=0.13 *P*=0.001	Same *P*>0.05	Less decrease in partial Δ=18 *P*<0.001	12	Conventional=40 eyes Partial**=40 eyes
Current study	RCT	Δ=−0.01 Conventional Δ=−0.01 Daya *P*=0.259	Δ=−0.04 Conventional Δ=−0.02 Daya *P*=0.937	Δ=−0.1 Conventional Δ=−0.02 Daya *P*=0.868	Δ=−23 Conventional Δ=−2 Daya *P*=0.0001	12	Conventional=34 Daya=30

[a]This study comprises patients operated with hypotonic and isotonic riboflavin. Only the results of the isotonic riboflavin were noted for comparison, *In this study, partial deepithelization procedure was performed with 4-5 vertical full-thickness stripes, 1-1.5 mm wide with 1 mm distance between them, **In this study, partial method was performed with three or four 1-mm-wide vertical strips, 1 mm apart from the central 7 mm of the cornea, and one horizontal strip from the inferior one-third of the cornea. Mean K: Mean keratometry, D: Diopter, BCVA: Best corrected visual acuity, UCVA: Uncorrected visual acuity, CCT: Central corneal thickness, RCT: Randomized clinical trial, Δ: Difference of changes

changes. In KCN, the epithelium at the apex of the cone becomes thinner and at the surrounding of the cone becomes thicker.[19-21] Thinning of the corneal apex is a compensatory mechanism to decrease the anterior stromal protrusion.[19] After CXL, an epithelial remodeling in the area of the protrusion and thinning of the cornea occurs, which leads to an increase in the epithelial thickness in this area.[19-21] Both mechanisms of strengthening in stromal collagen cross-linking and a slight increase in the epithelial thickness in the area of corneal thinning result in stopping the KCN progression. Reinstein *et al*. in a study on post-LASIK ectasia have described the difference between the thinnest and thickest points of the epithelium as an indicator for the corneal ectasia progression.[19] In our study, this indicator decreased after both CXL methods; however, the reduction in the epithelium-removal group was statistically significant. This result shows that epithelium-removal CXL has a better effect on altering the epithelium thickness in comparison to Daya CXL. In addition, we found that the mean inferior epithelial thickness was slightly more than the mean superior epithelial thickness in both groups. It seems that the epithelium in areas of significant corneal thinning is more affected by the CXL treatments.

This study was limited by a small and incomplete sample size and short follow-up time. A longer follow-up with large sample size will be needed to investigate and compare the visual outcome and keratometric indices between the two methods.

Parker *et al*. recommended that only cooperative patients with good family support are acceptable candidates for epithelium-off CXL.[20] We believe that it is reasonable to recommend epithelium-disruption CXL in patients with thinner cornea, high risk for epithelial healing, and more prone to complications, such as patients with an eye rubbing habit and pediatrics. Otherwise, considering the equal efficacy in keratometric indices in both methods, due to better efficacy of epithelium-removal CXL regarding epithelium remodeling as a compensatory mechanism for halting of KCN progression, the epithelium-removal CXL remains the first choice in other patients.

In conclusion, the results of this study showed that although epithelium-removal CXL is a more painful method than epithelium-disruption CXL, it produced better epithelial thickness profiles. Follow-up results after 12 months showed that there was no superiority between the two groups for UCVA, BCVA, front K-max, front mean K, and back K-max, but the epithelium-disruption CXL produced better results with respect to the thinnest point on pachymetry and SE than the epithelium-removal CXL.

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Conflicts of interest

There are no conflicts of interest.

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