Matched Comparison Study of Total and Partial Epithelium Removal in Corneal Cross-linking

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ABSTRACT

PURPOSE: To compare the 1-year results of total versus partial epithelium removal in corneal cross-linking in the treatment of progressive keratoconus.

METHODS: This retrospective study compared the results of total (the total group) versus partial (the partial group) approaches of epithelium removal in corneal cross-linking. Eighty eyes of 65 patients (40 eyes in each group) were enrolled. The mean age of the participants was 25.48 ± 4.80 years and 62.5% were male. One-year changes in vision parameters, refraction, and Pentacam (Oculus Optikgeräte GmbH, Wetzlar, Germany) indices were compared between the two groups using repeated measures analysis of variance.

RESULTS: One year after corneal cross-linking, uncorrected distance visual acuity in the total and partial group improved by 0.13 ± 0.42 and 0.12 ± 0.36 logMAR (P = .447), respectively, and corrected distance visual acuity improved by 0.00 ± 0.19 and 0.13 ± 0.20 logMAR (P = .001), respectively. Spherical equivalent decreased by 0.44 ± 1.25 diopters (D) in the total group and 0.56 ± 1.47 D in the partial group (P = .710). The decrease in maximum keratometry was 0.39 ± 0.93 and 0.01 ± 0.95 D in the total and partial group, respectively (P = .037), and the decrease in mean keratometry was 0.42 ± 0.93 and 0.00 ± 0.65 D (P = .015), respectively. Central corneal thickness decreased by 18.39 ± 20.66 μm in the total group and 0.11 ± 13.29 μm in the partial group (P < .001).

CONCLUSIONS: One year after corneal cross-linking, both approaches showed similar results in terms of uncorrected distance visual acuity. With the partial approach, there was slightly better corrected distance visual acuity improvement and central corneal thickness maintenance, but slightly better corneal flattening was achieved with the total removal. Long-term studies are needed to compare these two approaches in terms of stability of results and stopping the progression of keratoconus.

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Corneal cross-linking (CXL) with riboflavin and ultraviolet-A was first developed by Wollensak et al. for the treatment of progressive keratoconus.[1] In this procedure, the corneal epithelium, which is a barrier for riboflavin molecules, is removed to enhance the permeation and accelerate the saturation of riboflavin.[2] CXL is an oxygen-dependent process[3] and the intact epithelium might represent an additional barrier to oxygen molecules. Different approaches of epithelium removal in CXL have been assessed. The epithelium is removed totally in the standard method,[1] but some practitioners remove it partially.[4,5] Others use a femtosecond laser to create an instrastromal pocket for injecting riboflavin and the corneal surface remains intact,[6] and some use excimer laser transepithelial phototherapeutic keratectomy (PTK).[7]

There are pros and cons to each method. For example, with the epithelium-off approach, riboflavin saturation is ensured. Transepithelial PTK is one of the epithelium-off approaches that has shown promising visual and refractive results compared to the manual method.[7] Riboflavin saturation directly and linearly affects the amount of ultraviolet absorption and formation of covalent bonds.[2] When the epithelium is removed partially, there is less corneal damage and faster reepithelialization. In the epithelium-on approach, postoperative pain is significantly reduced because epithelium injury is minimized. However, the ultimate goal is to ensure stable treatment results. In this study, we retrospectively compared the total and partial approaches of epithelium removal.

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PATIENTS AND METHODS

This study retrospectively assessed and compared treatment results with two approaches of total versus partial epithelium removal in CXL. Eighty eyes of 65 patients with keratoconus (40 eyes in each group) were enrolled. Of the enrolled patients, 62.5% were male and 33.7% used contact lenses. All patients showed signs of progressive keratoconus, defined as an increase of at least 1.0 diopter (D) in maximum keratometry (K_{max}), manifest cylinder, or spherical equivalent, or losing two or more lines of corrected distance visual acuity (CDVA) over the past 12 months. Patients were 15 to 35 years old (mean age: 25.48 ± 4.80 years), K_{max} was less than 55.0 D in all cases, and central corneal thickness (CCT) was 450 µm or greater.

The protocol of the study was approved by the local Noor Review Board, Tehran, Iran. Data extraction from patient charts was performed anonymously using chart IDs. Uncorrected distance visual acuity (UDVA) and CDVA were measured using Snellen charts, and refraction and spherical equivalent were based on retinoscopy (ParaStop HEINE BETA 200; HEINE Optotechnik, Herrsching, Germany). Corneal topography was performed using Pentacam (Oculus Optikgeräte GmbH, Wetzlar, Germany), from which minimum keratometry (K_{min}), K_{max}, and CCT were extracted. Mean keratometry was calculated from K_{max} and K_{min}.

SURGICAL TECHNIQUES

Total Epithelium Removal (Total Group). After local anesthesia using proparacaine hydrochloride 0.5%, the central 9.0 mm of the corneal epithelium were removed manually using a hockey knife. After removing the eyelid speculum, riboflavin drops (0.1% in 20% dextran) (Streuli Pharmaceuticals, Uznach, Switzerland) were instilled onto the corneal surface at 3-minute intervals for half an hour. For all surgical cases, intraoperative corneal thickness was performed before irradiation. No patient had a corneal thickness less than 400 µm during the procedure, so none required swelling solutions. After ensuring the presence of riboflavin, by observing a yellow tinge in the anterior chamber, irradiation at a wavelength of 365 µm and an intensity of 3 mW/cm^2 commenced from a distance of 5 cm using the UV-X 1,000 system (IROC, Zürich, Switzerland). Riboflavin instillation continued every 3 minutes during the 30 minutes of irradiation. At the end of this stage, the corneal surface was rinsed with sterile balanced saline solution, a soft bandage contact lens (Night & Day, Ciba Vision, Duluth, GA) was applied, and levofloxacin eye drops were instilled. Postoperative medication included levofloxacin eye drops four times daily, betamethasone 0.1%, and preservative-free artificial tears (hypromellose) as required. Patients were examined at days 1 and 3 after the procedure, and the bandage lens was removed once the epithelium had completely healed; otherwise, visits were continued daily. After removing the lens, levofloxacin was stopped and betamethasone was continued four times daily for 1 more week.

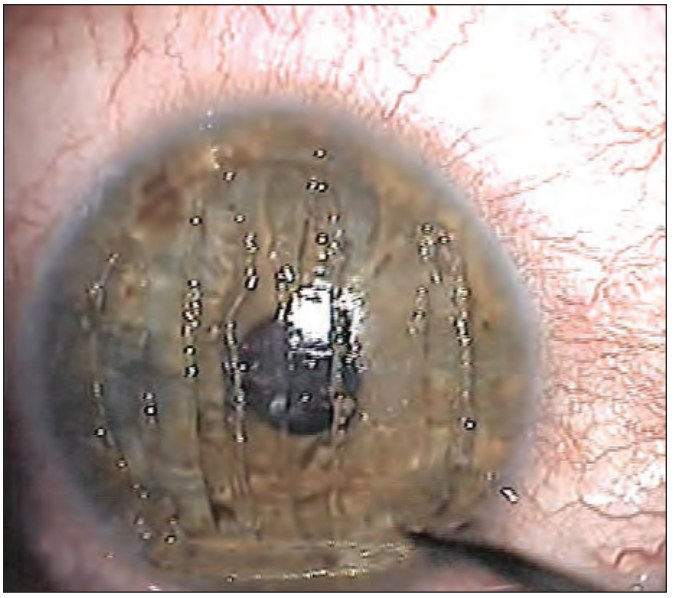

Figure 1. Partial epithelium removal method in corneal cross-linking.

Partial Epithelium Removal (Partial Group). The procedure, postoperative examinations, and medications were similar to those of the total group with the following modifications: after placing the eyelid speculum, epithelium was removed in 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 (**Figure 1**).

STATISTICAL ANALYSIS

Statistical analyses were performed using STATA software version 11 (StataCorp LP, College Station, TX). The trend of changes in indices was compared between the two groups using repeated measures analysis of variance and differences between before and 1 year after CXL using the paired *t* test. A *P* value of .05 was considered statistically significant.

RESULTS

The intergroup differences in baseline parameters were not statistically significant (**Table A,** available in the online version of this article). Intergroup differences in 6-month changes in UDVA ($P = .373$), CDVA ($P = .262$), spherical error ($P = .164$), K_{max} ($P = .293$), K_{min} ($P = .109$), mean keratometry ($P = .613$), and CCT ($P = .159$) were not significant. However, changes in cylinder error ($P = .052$) and spherical equivalent ($P = .048$)

TABLE 1

Comparison of 1-Year Changes in Vision and Refraction Parameters Between the Total and Partial Groups

Epithelium Removal	Preoperative Mean ± SD (Range)	Postoperative Mean ± SD (Range)		P^a	P^b
		6 Months	12 Months		
UDVA (logMAR)					
Total	0.84 ± 0.52 (0.00 to 1.80)	0.83 ± 0.52 (0.05 to 2.00)	0.70 ± 0.48 (0.00 to 2.00)	.047	.447
Partial	0.69 ± 0.52 (0.00 to 2.00)	0.59 ± 0.45 (0.00 to 2.00)	0.57 ± 0.38 (0.00 to 1.30)	.044	
CDVA (logMAR)					
Total	0.24 ± 0.19 (0.00 to 0.70)	0.23 ± 0.21 (0.00 to 1.00)	0.25 ± 0.23 (0.00 to 1.00)	.602	.001
Partial	0.32 ± 0.28 (0.00 to 1.00)	0.25 ± 0.31 (0.00 to 1.90)	0.19 ± 0.14 (0.00 to 0.50)	< .001	
Sphere (D)					
Total	-1.81 ± 2.27 (-10.00 to 1.00)	-1.71 ± 2.54 (-10.00 to 1.00)	-1.44 ± 2.39 (-11.00 to 1.25)	.084	.186
Partial	-1.70 ± 2.15 (-8.00 to 1.00)	-1.09 ± 1.55 (-7.00 to 1.00)	-1.32 ± 1.51 (-6.00 to 0.90)	.081	
Cylinder (D)					
Total	-2.73 ± 1.57 (-6.00 to 0.00)	-2.97 ± 1.74 (-6.00 to 0.00)	-2.58 ± 1.77 (-6.00 to 0.00)	.267	.109
Partial	-3.17 ± 2.20 (-8.50 to 0.00)	-2.71 ± 2.12 (-7.00 to 0.00)	-2.81 ± 1.90 (-6.00 to 0.00)	.104	
SE					
Total	-3.18 ± 2.60 (-14.50 to 0.00)	-3.20 ± 2.85 (-14.50 to 0.00)	-2.73 ± 2.69 (-13.50 to 0.00)	.027	.710
Partial	-3.28 ± 2.22 (-13.00 to 0.00)	-2.44 ± 2.03 (-11.50 to 0.75)	-2.73 ± 1.71 (-10.00 to 0.90)	.027	

SD = standard deviation; UDVA = uncorrected distance visual acuity; CDVA = corrected distance visual acuity; D = diopters; SE = spherical equivalent
[a]Based on difference between the averages before and 1 year after surgery in each group using paired t test.
[b]Based on intergroup comparison of the trend of changes.

were significantly different, and showed a descending trend between 6 and 12 months.

Visual Outcomes

One-year trends of changes in vision and refraction parameters were not statistically significant between the two groups except for CDVA (**Table 1**). CDVA changed by 0.13 ± 0.20 and 0.00 ± 0.19 logMAR in the partial and total groups, respectively (P = .001). The safety index for the total and partial groups was 0.63 ± 0.42 (range: 0.00 to 2.00) and 1.30 ± 1.35 (range: 0.00 to 6.67) (P = .007), respectively, and the efficacy index was 3.10 ± 4.92 (range: 0.00 to 9.00) and 4.08 ± 4.42 (range: 0.00 to 8.50), respectively (P = .377) (**Figure 2**).

Refractive Outcomes

One-year trends of changes in spherical and cylinder error showed no significant changes and were similar between the two groups. Spherical equivalent had a similar statistically significant decrease in both groups (**Table 1**).

Topographic Outcomes

At 1 year, K_{max} had significantly decreased in the total and partial group, respectively. K_{min} also had a statistically significant decrease in the total group and did not change in the partial group. K_{min} changes were significantly different between the two groups. The same trend was observed in mean keratometry, which decreased in the total group but had almost no change in the partial group. The decrease in CCT was significantly greater in the total group than in the partial group (P < .001) (**Table 2**).

DISCUSSION

This study retrospectively compared 1-year follow-up results of the two approaches of total and partial removal of corneal epithelium in CXL. During CXL, the corneal epithelium, which is a barrier for riboflavin molecules and oxygen, is removed so that riboflavin concentration can reach a level that would create new covalent bonds in collagen when exposed to ultraviolet-A.[1] Considering the molecular weight of riboflavin (376.37 g/mol), it is suggested that intact epithelium can impede riboflavin absorption and increase ultraviolet absorption in the cornea up to 95%.[8] In vitro studies have shown that ultraviolet absorption increases linearly up to a concentration of 0.04%,[2] riboflavin reduces the keratocyte cytotoxicity effect of ultraviolet-A up to ten times,[9] and without the use of riboflavin, the lens would absorb 50% of the ultraviolet-A at 365 µm.[10] Therefore, one could assume that stromal saturation with riboflavin has both

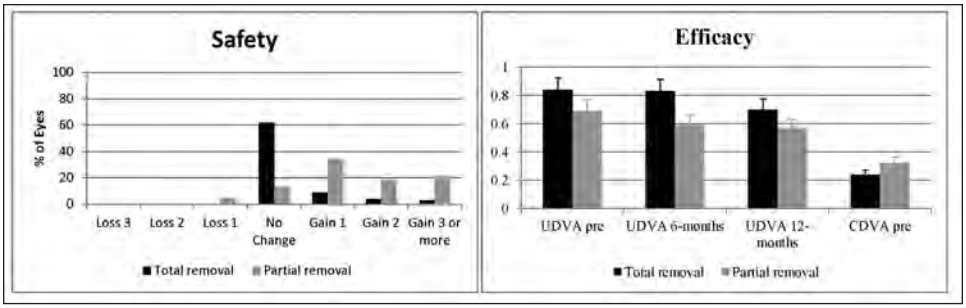

Figure 2. One-year changes in uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) in partial and total epithelium removal in corneal cross-linking.

TABLE 2

Comparison of 1-Year Changes in Pentacam Indices Between the Total and Partial Groups

Epithelium Removal	Preoperative Mean ± SD (Range)	Postoperative Mean ± SD (Range)		P^a	P^b
		6 Months	12 Months		
K_{max} (D)					
Total	48.69 ± 3.40 (41.10 to 55.50)	49.00 ± 3.61 (41.60 to 56.20)	48.30 ± 3.59 (41.00 to 54.60)	< .001	.037
Partial	49.40 ± 3.51 (42.90 to 57.30)	49.51 ± 3.53 (42.60 to 57.20)	49.37 ± 3.21 (43.50 to 55.50)	.518	
K_{min} (D)					
Total	45.31 ± 3.06 (40.30 to 53.70)	45.18 ± 3.26 (39.40 to 54.20)	44.86 ± 3.27 (38.80 to 53.30)	.044	.039
Partial	45.14 ± 2.65 (40.80 to 50.20)	45.37 ± 3.15 (40.60 to 54.10)	45.19 ± 2.63 (41.00 to 50.90)	.243	
K_{mean} (D)					
Total	47.00 ± 3.06 (40.70 to 54.60)	47.09 ± 3.28 (40.50 to 55.20)	46.58 ± 3.24 (39.90 to 53.95)	< .001	.015
Partial	47.27 ± 2.87 (41.85 to 53.15)	47.44 ± 3.18 (41.60 to 55.65)	47.28 ± 2.74 (42.25 to 53.00)	.251	
Topographic astigmatism (D)					
Total	3.38 ± 2.07 (0.00 to 8.30)	3.82 ± 2.10 (0.00 to 8.00)	2.22 ± 7.94 (-2.80 to 8.20)	.258	.405
Partial	4.26 ± 2.40 (0.50 to 10.00)	4.15 ± 2.11 (0.30 to 9.80)	4.17 ± 2.11 (0.00 to 9.80)	.713	
CCT (μm)					
Total	494.7 ± 32.9 (410.0 to 550.0)	482.5 ± 35.1 (387.0 to 555.0)	476.3 ± 37.7 (385.0 to 546.0)	< .001	< .001
Partial	482.6 ± 29.2 (412.0 to 547.0)	474.4 ± 29.0 (427.0 to 542.0)	482.4 ± 28.5 (444.0 to 553.0)	.960	

SD = standard deviation; K_{max} = maximum keratometry; D = diopter; K_{min} = minimum keratometry; K_{mean} = mean keratometry; CCT = central corneal thickness
[a]Based on difference between the averages before and 1 year after corneal cross-linking in each group using paired t test.
[b]Based on intergroup comparison of the trend of changes.
The Pentacam is manufactured by Oculus Optikgeräte GmbH, Wetzlar, Germany.

efficacy and safety implications. In the partial removal method, there is concern about a potential lack of riboflavin permeation and insufficient oxygen. Because horizontal propagation of riboflavin in the cornea is faster than vertical propagation, removing a horizontal strip during CXL can help riboflavin penetrate the epithelium-on zone and saturate the stroma. We examined patients at the slit lamp after instilling riboflavin drops ten times to ensure saturation of the corneal stroma with riboflavin before irradiation. The penetration of riboflavin to anterior chamber indicates that the corneal stroma is saturated. Also, we used the standard protocol of instillation of riboflavin, 3-minute intervals for half an hour, confirmed in previous studies.[11]

Visual Outcomes

In our study, the mean improvement in UDVA was comparable in both groups and similar to previous studies using the total removal approach.[12,13] In terms of CDVA, there was no loss of vision in the total removal group. Compared to 1-year results with transepithelial PTK in the study by Kymionis et al.,[7,14] UDVA results were less impressive in both of our groups; this could be due to the corneal smoothing effect with their method. Changes in keratometry support this hypothesis. However, the CDVA in both of our groups was not clinically significantly different from the mechanical or transepithelial PTK groups in the study by Kymionis et al.[7,14] In their study, CDVA changes were statistically significant

in the transepithelial PTK group (0.11 logMAR) and insignificant in the mechanical group (0.07 logMAR), but improvements seem clinically modest in both groups. Overall, both total and partial approaches appear to have similar impact on UDVA, and methods such as transepithelial PTK can be used to improve it. However, in terms of their effect on corneal irregularity and improving CDVA, the partial approach seems to be superior. The improved vision observed in the partial group could be due to less corneal haze.

Refractive Outcomes

In the current study, refraction and cylinder error remained stable in both groups, and showed no significant change after CXL. Although we need long-term studies to assess the stability of indices, our long-term study of CXL with partial removal[4] showed stable refraction and no progression more than 5 years after surgery. In the study by Kymionis et al.,[14] spherical equivalent had a statistically insignificant decrease of 0.8 D at 1 year, which is clinically negligible for patients with keratoconus. Another point is that irregular changes in these indices at the follow-up visits of the current study cast doubt on the repeatability of refraction: in keratoconus, even after CXL, the scissors reflex makes it difficult to determine the exact refraction. Davis et al.[15] showed weak repeatability for refraction in patients with keratoconus. We are currently conducting a study to examine the repeatability of refraction before and after CXL.

We observed no intergroup difference in refraction indices at 12 months after CXL. This could be indicative of proper formation of covalent bonds in the stroma and cessation of disease progression in both groups. Using intraoperative optical coherence tomography, Malhotra et al.[16] demonstrated that up to an hour after surgery, covalent bonds form less deep in the cornea in the "epithelium-on" area than the "epithelium-off" area, which might not cause significant clinical differences. Population differences may also play a role. In studying Asian populations, Saffarian et al.[17] and El-Raggal et al.[18] reported changes of less than 1.0 D in these indices. Other populations reported changes of greater than 1.0 D.[6,12]

Topographic Outcomes

Changes in keratometry readings were significantly different between the two groups. Six months after surgery, increased K_{max} and K_{min} were observed in both groups, which was tangibly greater in the total group. This can be due to CXL-associated corneal haze; Greenstein et al.[19] demonstrated that CXL-associated corneal haze, which is indicative of proper intra-fibril reactions in the corneal stroma, is associated with a higher K_{max}. One year after CXL, both K_{min} and K_{max} were significantly different between the two groups: we observed a decrease in the total group and no change in the partial group. Thus, we could say that, whereas disease progression stopped with the partial method, statistically significant improvement and corneal flattening was achieved with the total method. The difference was clinically modest and less than 0.5 D.

Our findings demonstrated that at 6 months, CCT had decreased similarly in both groups. But 1 year after surgery, CCT in the partial group returned to the preoperative thickness and remained stable. In contrast, it continued to decrease in the total group. Rechichi et al.,[5] who also used epithelial disruption, showed corneal thickness stability 6 to 12 months after surgery. Considering the method of epithelium debridement in the epithelium-on approach, the corneal thickness is expected to have better epithelial retention compared to the epithelium-off approach. We found no significant CCT change in our partial group either. However, in the total group, reduced thickness was also observed at 1 year. Decreases in CCT despite corneal flattening have been demonstrated in some studies,[17,20,21] and it might be necessary to evaluate Pentacam CCT repeatability after CXL. More accurate comparisons on corneal cellular changes could have been drawn if endothelial cell count data were available.

Our retrospective results suggest that both partial and total epithelium removal CXL approaches stop keratoconus progression, and they maintain UDVA and refraction in a similar manner. However, CDVA improvement was slightly better in the partial group. In terms of corneal flattening, the total removal method is slightly superior to the partial method. In light of these results and considering faster reepithelialization, partial removal could replace the total removal approach in certain subpopulations of keratoconus (ie, in milder cases and those with thinner, more regular corneas). Considering the limitations of the study and being retrospective, randomized clinical trials with long-term follow-ups are needed to draw conclusions with absolute certainty.

Author Contributions

Study concept and design (HH, MM, SA); data collection (HH, MM); analysis and interpretation of data (FH, SA); drafting of the manuscript (SA); critical revision of the manuscript (FH, HH, MM); statistical expertise (SA); supervision (HH)

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TABLE A

Comparison of Baseline Parameters Between the Total and Partial Groups

Parameter	Total Group (40 Eyes) Mean ± SD (Range)	Partial Group (40 Eyes) Mean ± SD (Range)	*P*[a]
Age (y)	24.88 ± 4.38	26.13 ± 5.21	.248
UDVA (logMAR)	0.84 ± 0.52 (0.00 to 1.80)	0.69 ± 0.52 (0.00 to 2.00)	.210
CDVA (logMAR)	0.24 ± 0.19 (0.00 to 0.70)	0.32 ± 0.28 (0.00 to 1.00)	.119
Sphere (D)	-1.81 ± 2.27 (-10.00 to 1.00)	-1.70 ± 2.15 (-8.00 to 1.00)	.821
Cylinder (D)	-2.73 ± 1.57 (-6.00 to 0.00)	-3.17 ± 2.20 (-8.50 to 0.00)	.312
MRSE (D)	-3.18 ± 2.60 (-14.50 to 0.00)	-3.28 ± 2.22 (-13.00 to 0.00)	.844
K_{max} (D)	48.69 ± 3.40 (41.10 to 55.50)	49.40 ± 3.51 (42.90 to 57.30)	.458
K_{min} (D)	45.31 ± 3.06 (40.30 to 53.70)	45.14 ± 2.65 (40.80 to 50.20)	.761
K_{mean} (D)	47.00 ± 3.06 (40.70 to 54.60)	47.27 ± 2.87 (41.85 to 53.15)	.774
CCT (μm)	494.7 ± 32.9 (410.0 to 550.0)	481.6 ± 29.2 (412.0 to 547.0)	.121

SD = standard deviation; UDVA = uncorrected distance visual acuity; CDVA = corrected distance visual acuity; D = diopter; MRSE = manifest refraction spherical equivalent; K_{max} = maximum keratometry; K_{min} = minimum keratometry; K_{mean} = mean keratometry; CCT = central corneal thickness

[a]*Based on independent sample* t *test.*