# Mechanical Epithelial Debridement *versus* Transepithelial Phototherapeutic Keratectomy Followed by Accelerated Corneal Collagen Crosslinking for Progressive Keratoconus

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## ABSTRACT

**Objective:** To compare the visual and topographic outcomes between mechanical epithelial debridement followed by accelerated corneal collagen cross linking (CXL) *vs.* transepithelial phototherapeutic keratectomy followed by accelerated CXL for treatment of progressive keratoconus.

**Study Design:** Quasi experimental study.

**Place and Duration of the Study:** Armed Forces Institute of Ophthalmology (AFIO), National University of Medical Sciences, Rawalpindi, Pakistan, from December 2020 to December 2021.

**Methodology:** On the basis of surgical technique used, patients were divided into two groups, Group A comprising of twenty eyes that underwent mechanical epithelial removal followed by accelerated CXL, and Group B comprising of twenty-two eyes that underwent transepithelial phototherapeutic keratectomy (t-PTK) followed by accelerated CXL. All variables were recorded preoperatively and 6 and 12 months postoperatively and included uncorrected visual acuity (UCVA), corrected distance visual acuity (CDVA), MRSE (manifest refraction spherical equivalent), and keratometric indices (flat K, steep K, Kmax , mean K, thinnest pachymetry, KPI, K prob, CLMIaa, and I-S).

**Results:** Forty-two eyes of twenty-nine patients were included in the study and were divided into two groups; Group A (mechanical epithelial removal followed by accelerated CXL) and Group B (t-PTK followed by accelerated CXL). The visual acuity improved in both the groups at 6 and 12 months, with more significant improvement in Group B in both UCVA (p=0.005) and CDVA (p=0.004) parameters. Keratometric outcomes showed significant differences in median values for flat K (p=0.048) and thinnest pachymetry (p=<0.001) in Group A, while significant difference in Kmax (p=0.024) and thinnest pachymetry (p=<0.001) in Group B. At 6 and 12 months, the CLMIaa, PPK, and I-S values were significantly lower in Group B (p=0.002 for all three indices).

**Conclusion:** Transepithelial PTK followed by accelerated CXL yielded better outcomes regarding visual acuity and keratomertic indices as compared to mechanical epithelial removal followed by accelerated CXL and did not show any significant decrease in corneal pachymetry.

**Key Words:** *Mechanical, Corneal Collagen Crosslinking (CXL), Transepithelial, Phototherapeutic keratectomy, Keratoconus.*

**How to cite this article:** Humayun S, Tahir A, Ishaq M, Arzoo S, Shah AA. Mechanical Epithelial Debridement *versus* Transepithelial Phototherapeutic Keratectomy Followed by Accelerated Corneal Collagen Crosslinking for Progressive Keratoconus. *J Coll Physicians Surg Pak* 2023; **33(11)**:1264-1270.

## INTRODUCTION

Keratoconus is the most common progressive, self-limiting, asymmetrical, bilateral keratectasia with progressive corneal stromal thinning resulting in irregular astigmatism and visual deterioration in young population.[1]

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*Received: March 14, 2023; Revised: July 05, 2023; Accepted: October 11, 2023*
*DOI: https://doi.org/10.29271/jcpsp.2023.11.1264*

The rate of disease progression varies between individuals but usually progression halts within 20 years of disease commencement.[2] Corneal topography and tomography are the exceptional diagnostic tools that are non-contact based and aid in the disease diagnosis and progression. Advanced softwares including Enhanced Reference Surface and Belin-Ambrosio Enhanced Ectasia display assist in early detection of the disease.[3]

Previously, treatment of keratoconus was focused on possible refractive correction with the help of spectacles, soft and rigid gas permeable contact lenses, and penetrating keratoplasty was considered for advanced stage disease.[4] The advent of corneal collagen crosslinking (CXL) as a minimally invasive procedure in 1997 and the unrivalled buildout in the disease management in the last two decades has shifted the treatment paradigm of kera-

toconus and other corneal ectatic disorders.[5] In the photopolymerisation process, riboflavin acts as a photosensitizer and when proceeded by Ultraviolet A (UVA) radiation, the formation of intrafibrillar and interfibrillar bonds is enhanced in corneal stromal matrix.[6] The effectiveness of CXL highly relies on the ability of riboflavin to do corneal stromal saturation.[7] The hydrophilic nature and large molecular size of riboflavin cause hindrance in its passing through intact epithelium.[8] Previously various methods have been used for epithelial removal including rotating brush, scalpel, and use of ethyl alcohol. The surgeon's proficiency in manually removing the epithelium with intact underlying bowman's layer is the key to success of these procedures. However, the use of sharps resulted in damaging of Bowman's layer and cragged epithelium.[9] Ethyl alcohol, on the other hand, promotes easy and even epithelial debridement without damaging the Bowman's layer but it has been reported to have cytotoxic effects on keratocytes which after UVA radiation exposure are reduced in number.[10]

Excimer laser transepithelial phototherapeutic keratectomy (t-PTK) is a treatment modality for superficial corneal surface pathologies as it removes epithelium and also smooths out the irregular anterior cornea.[11] PTK removes epithelium at a constant pre calculated depth and selectively shaves the tip of the cone, thus, helps in improving visual acuity. A very limited data of comparison of Pakistani population is available in regards to outcome of different epithelial removal techniques in CXL. The objective of this study is to compare visual, refractive, and topographic outcomes in patients with progressive keratoconus who underwent mechanical epithelial removal and those who had t-PTK followed by accelerated CXL.

## METHODOLOGY

This was a quasi experimental study conducted at the Armed Forces Institute of Ophthalmology, Rawalpindi, from December 2020 to December 2021. Minimum sample size was 40 (20 eyes in each group), which was calculated using WHO sample size calculator with 95% confidence interval. After seeking approval from the hospital ethical review committee, a total of 42 patients with progressive keratoconus were included in this study according to nonprobability consecutive sampling and were divided into two groups. Group A had the eyes who underwent mechanical epithelial removal followed by accelerated CXL and Group B included those who had t-PTK followed by accelerated CXL. Inclusion criteria was age of 12 years or older with progressive keratoconus and corneal pachymetry of more than 400 µm at the thinnest point. Exclusion criteria was history of corneal trauma or surgery, use of contact lens, pregnancy, lactation, active keratitis and any other anterior segment pathology including corneal scarring. Keratoconus was defined as progressive after two tomography scans (taken 6 months apart) showing increase in spherical equivalent of 0.75 D, change in astigmatism of 1.00 D and increase in maximum keratometry of 0.75 D.

All patients had preoperative assessment comprising of demographic details, history, ocular examination including uncorrected visual acuity (UCVA), corrected distance visual acuity (CDVA), MRSE (manifest refraction spherical equivalent) measurements (converted to logMAR unit for analysis), anterior and posterior segment slit lamp examination and corneal analysis using Galilei 4, consisting of dual Scheimpflug tomography and Placido topography (Galilei, Ziemer Ophthalmic Systems AG, Biel, Switzerland). Postoperative data were collected at 6 and 12 months which included UCVA, CDVA, MRSE, refractive astigmatism, flat K (keratometry in flat meridian), steep K (keratometry in steep meridian), mean K (mean keratometry), Kmax (maximum keratometry), topographic astigmatism, thinnest corneal pachymetry, KPI (keratoconus prediction index), Kprob (keratoconus probability index), CLMIaa (cone location magnitude index anterior axial), PPK (percentage progression of keratoconus), and I-S (inferior-superior).

All procedures were performed at AFIO by the same surgeon in operation theatre under aseptic conditions. Other than the technique of epithelium removal, CXL procedure was the same in both groups. In Group A, proparacaine hydrochloride 0.5% eye drop (Alcon Laboratories) was instilled before the procedure for topical anaesthesia. Central 8 mm of corneal epithelium was mechanically removed with spatula sparing 1 mm from the limbus. Riboflavin (0.1% solution of Vitamin B2, 1.0% HPMC, [Peschke M, Peschke Trade GmbH]) was instilled on the corneal stroma, 1 drop every 2 minutes for 30 minutes (AC must be yellow under blue light). Pachymetry was then done after 30 minutes to ensure corneal thickness of more than 400 microns before applying Ultraviolet A (UVA) radiation. UVA radiation was then delivered using UVA optical system (Vario, CCL-365, wavelength 365 nm) for 10 minutes at surface irradiance of 9 mW/cm$^2$ (5.4 J/cm$^2$ surface dosage) (Accelerated Protocol). During irradiation, riboflavin drops were instilled every 2 minutes to maintain corneal saturation with riboflavin. Cornea was then washed thoroughly with balanced salt solution, and bandage contact lens was applied after the completion of procedure.

In Group B, topical anaesthesia was done with proparacaine hydrochloride 0.5% eye drops (Alcon Laboratories) instilled before the procedure. Excimer laser t-PTK (EX-500 Wavelight Technologies GmbH Erlangen Germany) was done in 7mm optical zone to remove corneal epithelium with intended depth of 50 µm. Mitomycin C (0.02%) soaked triangular sponge was applied on stromal bed in all patients after t-PTK for 30-40 seconds. It was then thoroughly washed with balanced salt solution. Rest of the CXL procedure was the same as above (Cretan protocol).

Post-procedure medication included topical antibiotic and steroid combination (tobramycin and dexamethasone 0.3%/0.1% w/v eye drops) and topical lubricant (combination of polyethylene glycol (PEG 400) 4 mg/ml and propylene glycol 3 mg/ml eye drops) thrice daily for 3 weeks. BCL was removed on 5$^{th}$ or 6$^{th}$ day after complete re-epithelialization of the cornea. Antibiotic plus steroid combination drops were replaced by fluoromethalone 0.1% (FML; Allergan, Inc.) eye drops three times daily on a tapering dose for next 6 weeks. Topical lubricants were continued three times daily for six months. Follow-

up was done on 6th day, 1, 3, 6, and 12 months. Corneal topography was done at 6 and 12 months.

The data for this study was analysed using IBM SPSS software (version 23.0). Keeping in view the small sample size, normality of data was checked visually and by Shapiro-Wilk test, both of which revealed that the spread of data was not normal. Keeping in the data distribution, the descriptive statistics were reported as median and IQR for continuous variables, while frequency and percentages were used for the categorical data. For comparison of continuous outcomes in Group A and B at baseline *vs.* 6-month, and 6-month *vs.* 1-year, the Wilcoxon signed rank test was used for the paired data. While for intergroup comparison of continuous outcome data, Mann-Whitney U test was used. The value of $p \leq 0.05$ was considered significant.

## RESULTS

There were 42 eyes of 29 patients included in the study. On the basis of surgical technique, patients were divided into two groups. Group A comprised of 20 (47.6%) eyes of 14 patients who underwent manual CXL technique, while Group B comprised of 22 (52.3%) eyes of 15 patients who underwent t-PTK CXL. The baseline clinical and demographic characteristics are given in Table I.

The pre- and post-procedure measurements for visual acuity, refractive, and keratometric biometrics were taken and compared as baseline *vs.* 6-month and 6-month *vs.* 12-month follow-ups. The visual acuity and refractive parameters were compared at 6-month with the baseline values, where significant changes were indicated in UCVA logMAR in both the groups while significant changes were seen in CDVA logMAR in Group B only. The visual acuity improved in both the groups after treatment at 6-month, with more significant improvement noticed in Group B where improvement occurred in both UCVA (p=0.005) and CDVA (p=0.004) parameters as shown in Table II. Other parameters including spherical equivalent and astigmatism remained more or less the same at 6-month after treatment in both the groups. Comparison of 6-month and 1-year data revealed no significant changes in any group in terms of visual acuity and refractive outcome. The intergroup comparison (Group A *vs.* Group B) showed no difference in median values of UCVA, CDVA, spherical equivalent, and astigmatism as shown in Table II. Figure 1 compares the UCVA logMAR between the two groups at baseline, 6-month and 1-year.

On the other hand, when keratometric outcomes including flat K, steep K, topographic astigmatism, Kmax, mean K, and thinnest pachymetry were compared between baseline and 6-month, significant differences in median values were noticed for flat K and thinnest pachymetry in Group A, while significant difference in Kmax and thinnest pachymetry was observed in Group B as shown in Table III. For 6-month and 1-year comparison in Group A, there was significant change in flat K only, while in Group B significant decrease was noticed in flat K and steep K median values. For intergroup comparison in terms of keratometric outcomes, significant difference was noticed in flat K at 6-month follow-up where the values were slightly higher among Group B patients (p=0.007). Similar trend was seen in steep K (p=0.028) while the Kmax was significantly higher in Group A (p=0.011) as given in Table III. All other parameters were more or less the same for both the groups with no significant differences being observed between Group A and B. Figure 2 gives comparison of Kmax while Figure 3 gives comparison of topographic astigmatism between two groups at baseline, 6-month, and 1-year.

For keratoconus indices outcomes, KPI values significantly increased at 6-month in Group A (p=0.037), while in Group B, KPI (p=0.008), CLMIaa (p=0.038), and I-S (p=0.022) were significantly reduced at 6-month. The intergroup comparison of groups A and B revealed that at 6-month and at 1-year, the CLMIaa, PPK, and I-S values were significantly lower in Group B (p=0.002 for each comparison) (p=0.005, p=0.010, and p=0.013, respectively) as compared to Group A as given in Table IV.

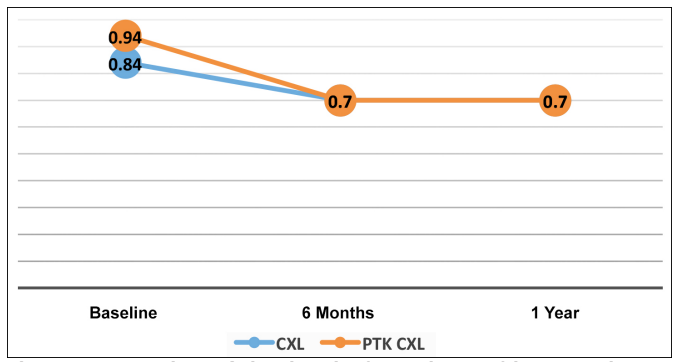


**Figure 1: Comparison of visual acuity (UCVA logMAR) between the two groups at baseline, 6-month and 1 year.**

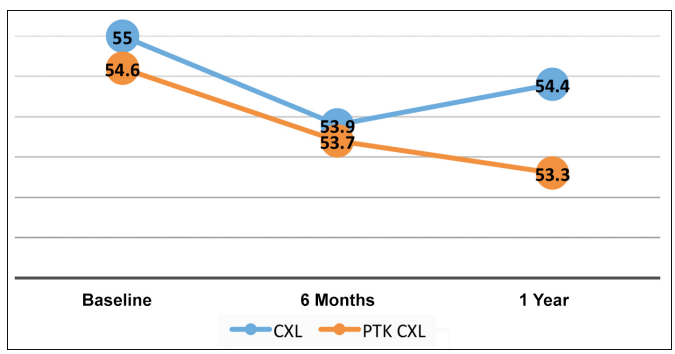


**Figure 2: Comparison of Kmax between two groups at baseline, 6-month and 1-year follow-up.**

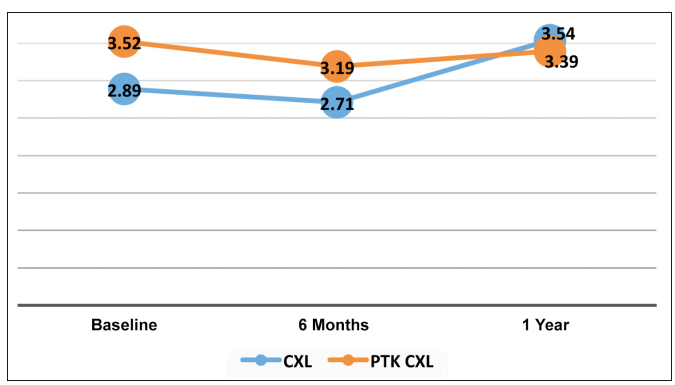


**Figure 3: Comparison of topographic astigmatism between two groups at baseline, 6-month and 1-year follow-up.**

**Table I: Baseline demographic and clinical characteristics (n=42).**

| | Overall Total (n=42) | Group A (n=20) | Group B (n=22) |
|---|---|---|---|
| Median age (IQR) | 15.0 (14.0, 21.0) | 16.5 (14.0, 21.0) | 15.0 (13.0, 21.2) |
| Gender | | | |
| Male | 29 (69.0%) | 14 (70.0%) | 15 (68.2%) |
| Female | 13 (31.0%) | 6 (30.0%) | 7 (31.8%) |
| Eye involved | | | |
| Right | 20 (47.6%) | 7 (35.0%) | 13 (59.1%) |
| Left | 22 (52.4%) | 13 (65.0%) | 9 (40.9%) |
| UCVA (log) Median (IQR) | 0.88 (0.58, 1.21) | 0.84 (0.55, 1.00) | 0.94 (0.66, 1.30) |
| CDVA (log) Median (IQR) | 0.35 (0.18, 0.49) | 0.35 (0.18, 0.52) | 0.35 (0.18, 0.49) |
| Astigmatism Median (IQR) | -3.87 (-5.50, -2.43) | -3.75 (-5.00, -2.31) | -3.87 (-5.62, -2.62) |
| MRSE Median (IQR) | -4.93 (-6.81, -2.96) | -4.75 (-5.50, -2.62) | -4.93 (-8.25, -3.06) |

*n = Number, Group A = Mechanical epithelial removal, Group B = t-PTK, UCVA = Uncorrected visual acuity, CDVA = Corrected distance visual acuity, log = LogMAR, p = p-value, Astigmatism = Refractive astigmatism, MRSE = Manifest Refraction Spherical Equivalent.*

**Table II: Comparison of visual acuity and refractive parameters at baseline, 6-month and 1-year follow-up.**

| | | Group A (n=20) | p* p** | Group B (n=22) | p* p** |
|---|---|---|---|---|---|
| UCVA log Median (IQR) | Baseline | 0.84 (0.55, 1.00) | 0.015 | 0.94 (0.66, 1.30) | 0.005 |
| | 6-month FU | 0.70 (0.48, 0.88) | 0.552 | 0.70 (0.400, 1.20) | 0.078 |
| | 1-year FU | 0.70 (0.40, 0.88) | | 0.70 (0.30, 1.00) | |
| CDVA log Median (IQR) | Baseline | 0.35 (0.18, 0.52) | 0.900 | 0.35 (0.18, 0.49) | 0.004 |
| | 6-month FU | 0.35 (0.10, 0.52) | 0.327 | 0.30 (0.18, 0.40) | 0.112 |
| | 1-year FU | 0.30 (0.12, 0.48) | | 0.30 (0.18, 0.40) | |
| MRSE Median (IQR) | Baseline | -4.75 (-5.50,-2.62) | 0.076 | -4.93 (-8.25, -3.06) | 0.052 |
| | 6-month FU | -3.50 (-6.00, -2.12) | 0.776 | -4.44 (-7.62, -3.50) | 0.289 |
| | 1-year FU | -3.75 (-5.87, -2.31) | | -4.75 (-6.62, -3.43) | |
| Astigmatism Median (IQR) | Baseline | -3.75 (-5.00, -2.31) | 0.859 | -3.87 (-5.62, -2.62) | 0.157 |
| | 6-month FU | -3.50 (-5.37, -2.62) | 0.339 | -4.12 (-5.00, -1.68) | 0.182 |
| | 1-year FU | -3.50 (-5.75, -2.50) | | -3.37 (-5.00, -1.87) | |

**Wilcoxon signed rank test baseline vs. 6-month, **Wilcoxon signed rank test 6-month vs. 1-year.*
*n = Number, UCVA = Uncorrected visual acuity, CDVA = Corrected distance visual acuity, log = LogMAR, p = p-value, MRSE = Manifest Refraction Spherical Equivalent, FU = Follow-up, Astigmatism = Refractive astigmatism.*

**Table III: Comparison of keratometric outcomes at baseline and 6-month follow-up, 6-month and 1-year follow-up.**

| | | Group A (n=20) | p* p** | Group B (n=22) | p* p** | p*** |
|---|---|---|---|---|---|---|
| Flat K Median (IQR) | Baseline | 44.5 (43.4, 48.2) | 0.048 | 46.7 (45.2, 48.7) | 0.434 | 0.148 |
| | 6-month FU | 44.2 (42.9, 46.4) | 0.038 | 46.6 (45.5, 48.0) | 0.002 | 0.007 |
| | 1-year FU | 44.6 (43.5, 46.7) | | 46.4 (44.5, 48.0) | | 0.113 |
| Steep K Median (IQR) | Baseline | 47.4 (45.5, 52.6) | 0.086 | 50.3 (48.6, 53.6) | 0.173 | 0.124 |
| | 6-month FU | 48.2 (45.3, 50.1) | 0.279 | 50.0 (48.6, 52.8) | 0.006 | 0.028 |
| | 1-year FU | 47.9 (46.1, 52.5) | | 49.8 (47.7, 52.8) | | 0.392 |
| Topographic astigmatism Median (IQR) | Baseline | 2.89 (1.84, 4.50) | 0.896 | 3.52 (2.01, 5.11) | 0.330 | 0.546 |
| | 6-month FU | 2.71 (2.19, 5.48) | 0.881 | 3.18 (2.29, 5.19) | 0.104 | 0.850 |
| | 1-year FU | 3.54 (2.26, 5.23) | | 3.39 (2.34, 4.73) | | 0.743 |
| Kmax Median (IQR) | Baseline | 55.0 (50.6, 58.9) | 0.287 | 54.6 (52.1, 58.4) | 0.024 | 0.920 |
| | 6-month FU | 53.9 (50.6, 57.1) | 0.279 | 53.7 (50.7, 57.1) | 0.408 | 0.830 |
| | 1-year FU | 54.4 (50.4, 56.8) | | 53.3 (50.1, 57.7) | | 0.791 |
| Mean K Median (IQR) | Baseline | 45.8 (44.7, 50.8) | 0.079 | 49.0 (46.7, 50.5) | 0.189 | 0.158 |
| | 6-month FU | 46.0 (44.3, 47.9) | 0.279 | 48.4 (46.8, 50.2) | 0.408 | 0.011 |
| | 1-year FU | 45.9 (44.8, 49.5) | | 48.0 (45.7, 49.9) | | 0.302 |
| Pachy thin Median (IQR) | Baseline | 450.5 (415.0, 457.0) | <0.001 | 449.5 (420.7, 472.2) | <0.001 | 0.473 |
| | 6-month FU | 400.5 (335.7, 430.2) | 0.314 | 422.5 (379.0, 443.2) | 0.130 | 0.110 |
| | 1-year FU | 408.0 (348.5, 430.2) | | 408.5 (366.7, 433.7) | | 0.529 |

**Wilcoxon signed rank test (paired data comparison baseline vs. 6-month), **Wilcoxon signed rank test (paired data comparison 6-month vs. 1-year), ***Mann-Whitney U test (intergroup comparison Group A vs. B).*
*n = Number, Pachy thin = Thinnest pachymetry, p= p-value, Flat K = Keratometry in flat meridian, Steep K = Keratometry in steep Meridian, Mean K = Mean keratometry, Kmax = Maximum keratometry, FU = Follow-up.*

**Table IV: Comparison of keratoconus indices outcomes at baseline, 6-month and 1-year follow-up.**

| | | Group A (n=20) | p* p** | Group B (n=22) | p* p** | p*** |
|---|---|---|---|---|---|---|
| KPI | Baseline | 94.35 (73.54, 100.0) | 0.037 | 96.8 (62.52, 100.0) | 0.008 | 0.526 |
| Median (IQR) | 6-month FU | 94.71 (63.11, 100.0) | 0.033 | 76.40 (49.85, 100.0) | 0.850 | 0.162 |
| | 1-year FU | 86.45 (46.77, 100.0) | | 72.50 (49.97, 100.0) | | 0.447 |
| K prob | Baseline | 100.0 (99.9, 100.0) | 0.233 | 100.0 (99.57, 100.0) | 0.477 | 0.490 |
| Median (IQR) | 6-month FU | 100.0 (99.7, 100.0) | 0.028 | 99.95 (96.37, 100.0) | 0.861 | 0.399 |
| | 1-year FU | 100.0 (95.62, 100.0) | | 99.85 (97.35, 100.0) | | 0.572 |
| CLMIaa | Baseline | 6.45 (4.61, 10.49) | 0.588 | 5.05 (2.61, 6.88) | 0.038 | 0.064 |
| Median (IQR) | 6-month FU | 6.56 (4.80, 10.15) | 0.695 | 4.13 (2.19, 5.32) | 0.548 | 0.002 |
| | 1-year FU | 6.55 (5.16, 9.83) | | 4.13 (2.24, 5.88) | | 0.005 |
| PPK | Baseline | 99.9 (96.6, 100.0) | 0.328 | 98.70 (31.27, 100.0) | 0.355 | 0.105 |
| Median (IQR) | 6-month FU | 99.9 (97.7, 100.0) | 0.859 | 91.2 (14.65, 99.22) | 0.629 | 0.002 |
| | 1-year FU | 99.99 (98.95, 100.0) | | 90.60 (17.42, 99.62) | | 0.010 |
| I-S | Baseline | 8.32 (5.81, 12.03) | 0.108 | 4.65 (3.33, 6.95) | 0.022 | 0.002 |
| Median (IQR) | 6-month FU | 7.57 (4.81, 11.02) | 0.007 | 4.04 (2.34, 6.19) | 0.445 | 0.002 |
| | 1-year FU | 6.51 (4.58, 9.35) | | 4.49 (2.88, 6.28) | | 0.013 |

**Wilcoxon signed rank test (paired data comparison baseline vs. 6-month), **Wilcoxon signed rank test (paired data comparison 6-month vs. 1-year), ***Mann-Whitney U test (intergroup comparison group A vs. B).*
*n = Number, KPI = Keratoconus prediction index, K prob = Keratoconus probability index, CLMIaa = Cone location magnitude index anterior axial, PPK = Percentage probability of keratoconus, I-S = Inferior-superior, p = p-value.*

## DISCUSSION

Keratoconus was considered to be a rare disease in the past but the epidemiology changed very rapidly. As the disease mostly affected the adults and showed progress till the 3rd or 4th decade of life, early detection and effective treatment were aimed at securing the productive members of a society and reducing the economic burden of disease in an affected population. Sporl *et al*. introduced the use of riboflavin drops in 1997 followed by Ultraviolet A radiation to enhance corneal stiffness.[12] Since then, many techniques of performing CXL had been devised for better control of the disease and improvement in visual quality. Numerous management modalities had been in practice but KC demands exigent treatment, that too, tailored according to the stage of disease. Furthermore, to reduce the photo toxicity risk in Dresden protocol, the high fluence accelerated protocol was introduced.[13] Epithelium-off technique gained popularity due to the enhanced penetration of riboflavin in corneal stroma, thus, producing promising output.[14] In a previous study, the efficacy of epithelium-off CXL in arresting the progression of KC was determined.[15] The conventional CXL protocol advocates the epithelial removal to be carried out mechanically. However, it can also be removed by transepithelial phototherapeutic keratectomy followed by CXL (Cretan protocol), first used by Kymionis *et al*. in 2010.[16] Following the first report, Kymionis *et al*. reproduced a study in 2012 showing comparison of the two techniques of epithelium removal in CXL (3 mW/cm$^2$, 5.4 J/cm$^2$, 30 min).[17]

In this study, the improvement in visual acuity was seen more in Group B, UCVA improved from 0.94±0.50 baseline to 0.70±0.30 postoperatively (25.5% improvement from baseline) at 6-month (p=0.005) and CDVA improved from 0.35±0.31 baseline to 0.30±0.22 postoperatively (14.2% improvement from baseline) at 6-month (p=0.004) as compared to Group A (UCVA 16.6% and CDVA showed no improvement). These results are similar to Kymionis *et al.* report in which 53% eyes after PTK CXL and 28% eyes after conventional CXL achieved UCVA ≥20/80 at their last follow-up.[17] In a retrospective case series of 40 eyes (aged less than 18 years), Sarac *et al*. reported that the initial visual and topography outcomes were better in t-PTK CXL than in mechanical CXL, however, there was no significant difference after analysis at 36 months between both groups.[18]

Another prospective, comparative case series of 30 eyes done by Grentzelos *et al*. showed improvement in UCVA (p = 0.018) and CDVA (p = 0.024) from baseline in Cretan protocol as compared to that in Dresden protocol.[19] Improvement in corneal astigmatism at 6- and 12-month after Cretan protocol as seen in this study (-3.5±3.10 logMAR baseline improved to -3.39±2.40 logMAR postoperatively) was in agreement with the results of Grentzelos *et al*.[19] In t-PTK, the anterior surface of the cornea became smooth along with the removal of stromal tissue above the ectatic cone. This caused visual acuity improvement as compared to mechanical epithelial removal.[20] On the contrary, Gaster *et al*. reported that both groups yielded similar outcomes at 24-month with improvement only in CDVA in t-PTK CXL group.[21] In a prospective study, Shakir *et al.* reported significant flattening of the steepest K value after CXL in 31 eyes under study.[22] In this study, in terms of keratometric outcome at 12-month, both the groups showed improvement in flat K, steep K and Kmax, with slightly better outcomes in Group B patients. Long-term comparison study done by Ozdas *et al*. also stated better kertometric outcomes in t-PTK CXL group.[23] The reduced corneal steepness (Kmax) in t-PTK CXL group was also reported by Gaster *et al*. in their study.[19,21] Ozdas *et al.* emphasised that their results were slightly different for Kmax due to the fact that their Kmax baseline values were slightly higher (54.41±4.42), however in the

current study, the values of Kmax were almost similar (54.6±6.80) preoperatively.[23] The thinnest pachymetry was also similar in both the groups in this study. Topographic astigmatism decreased from baseline in t-PTK CXL group as compared to mechanical epithelium removal followed by CXL, showing that these results were also analogous to the ones reported by Ozdas *et al*.[23]

When compared with the baseline values, a decrease in keratoconus prediction index of 8% and 25% was observed in patients of Group A and B, respectively. While considering the CLMIaa values, decrease of 18.8% from baseline value was seen in patients of Group B which was significantly greater than the result of Group A (0.7%). Rest of the indices including K prob and PPK had comparative results, however, I-S values were significantly lower after 1-year in Group A.

None of the patients in the study group had intra or postoperative complications except for slight haze in t-PTK group. In contrast to the report of Ozdas *et al*., excessive flattening was not seen in any patient in this study group.[23]

The effectiveness of the t-PTK CXL can be enhanced with the customisation of the t-PTK parameters (ablation depth and ablation zone) according to the patient's corneal epithelial mapping and corneal profile.

This study had few limitations, small sample size and lack of the division of cases according to KC severity. Despite these limitations, it provides valuable information on the refractive, visual, and topographic outcomes of mechanical and transepithelial PTK removal of epithelium for accelerated CXL in patients with progressive keratoconus. Further prospective large sample size studies are needed in the future for better long-term comparisons.

## CONCLUSION

Corneal collagen crosslinking is so far the most promising treatment modality for halting the progression of keratoconus. T-PTK CXL has yielded better outcomes regarding visual acuity and keratometric indices and has not shown any significant decrease in corneal pachymetry. This study supports the results of past studies showing superior outcomes in transepithelial phototherapeutic keratectomy followed by CXL as compared to mechanical epithelial removal in CXL.

**ETHICAL APPROVAL:**
An approval from the hospital's Ethical Review Committee of Armed Forces Institute of Ophthalmology was taken prior to the commencement of this research work in accordance with the principles of Declaration of Helsinki.

**PATIENTS' CONSENT:**
Written informed consents for collection, analysis, and publication of data were taken from every participant of this study.

**COMPETING INTEREST:**
The authors declared no competing interest.

**AUTHORS' CONTRIBUTION:**
SH: Contributed towards conception, design of work, and interpretation of data.
AT: Drafting of the research work and data analysis.
MI: Revisited the article critically for its important content, gave the final approval for the manuscript.
SA, AAS: Contributed towards data acquisition.
All authors approved the final version of the manuscript to be published.

## REFERENCES


1. Subasinghe SK, Ogbuehi KC, Dias GJ. Current perspectives on corneal collagen crosslinking (CXL). *Graefes Arch Clin Exp Ophthalmol* 2018; **256(8)**: 1363-84. doi: 10.1007/s00417-018-3966-0.
2. Uysal BS, Sarac O, Yaman D, Akcay E, Cagil N. Optical performance of the cornea one year following keratoconus treatment with corneal collagen cross-linking. *Curr Eye Res* 2018; **43(12)**:1415-21. doi: 10.1080/02713683.2018.1501802.
3. Bamdad S, Sedaghat MR, Yasemi M, Vahedi A. Sensitivity and specificity of belin ambrosio enhanced ectasia display in early diagnosis of keratoconus. *J Ophthalmol* 2020; **2020**:7625659. doi: 10.1155/2020/7625659.
4. Barnett M, Mannis MJ. Contact lenses in the management of keratoconus. *Cornea* 2011; **30(12)**:1510-6. doi: 10.1097/ICO.0b013e318211401f.
5. Spoerl E, Huhle M, Kasper M, Seiler T. Increased rigidity of the cornea caused by intrastromal cross linking. *Ophthalmologe* 1997; **94(12)**:902-6. doi: 10. 1007/s0034 7050219.
6. Roy SR, Ciro C, Carmine O. Corneal cross-linking: The science beyond the myths and misconceptions. *Cornea* 2019; **38(6)**:780-90. doi: 10.1097/ICO.0000000000001912.
7. Belin MW, Lim L, Rajpal RK, Hafezi F, Gomes JAP, Cochener B. Corneal cross-linking: Current USA status: Report from the cornea society. *Cornea* 2018; **37(10)**:1218-25. doi: 10.1097/ICO.0000000000001707.
8. Beckman KA, Gupta PK, Farid M, Berdahl JP, Yeu E, Ayres B, *et al*. ASCRS cornea clinical committee. Corneal crosslinking: Current protocols and clinical approach. *J Cataract Refract Surg* 2019; **45(11)**:1670-9. doi: 10.1016/j.jcrs.2019.06.027.
9. Hammer A, Rudaz S, Guinchard S, Kling S, Richoz O, Hafezi F. Analysis of riboflavin compounds in the rabbit cornea *in vivo*. *Curr Eye Res* 2016; **41(9)**:1166-72. doi: 10.3109/02713683.2015.1101141.

10. Fattah MA, Antonios R, Arba Mosquera S, Abiad B, Awwad ST. Epithelial erosions and refractive results after single-step transepithelial photorefractive keratectomy and alcohol-assisted photorefractive keratectomy in myopic eyes: A comparative evaluation over 12 months. *Cornea* 2018; **37(1)**:45-52. doi: 10.1097/ICO.0000000000001428.
11. Shalchi Z, Wang X, Nanavaty MA. Safety and efficacy of epithelium removal and transepithelial corneal collagen crosslinking for keratoconus. *Eye (Lond)* 2015; **29(1)**: 15-29. doi: 10.1038/eye.2014.230.
12. Spoerl E, Huhle M, Seiler T. Induction of cross-links in corneal tissue. *Exp Eye Res* 1998; **66(1)**:97-103. doi: 10.1006/exer.1997.0410.
13. Ting DSJ, Rana-Rahman R, Chen Y, Bell D, Danjoux JP, Morgan SJ, *et al*. Effectiveness and safety of accelerated (9mW/cm$^2$) corneal collagen cross-linking for progressive keratoconus: A 24-month follow-up. *Eye* 2019*;* **33(5)**:812-8. doi: 10.1038/s41433-018-0323-9.
14. Pedrotti E, Caldarella G, Fasolo A, Bonacci E, Gennaro N, Gregorio AD, *et al* Topographic and biomechanical changes after application of corneal cross-linking in recurrent keratoconus. *Int J Environ Res Public Health* 2019; **16(20)**: 1-9. doi: 10.3390/ijerph16203872.
15. Malik S, Humayun S, Nayyar S, Ishaq M. Determining the efficacy of corneal crosslinking in progressive keratoconus. *Pak J Med Sci* 2017; **33(2)**:389-92. doi: 10.12669/pjms.332.11690.
16. Kymionis GD, Grentzelos MA, Karavitaki AE, Kounis GA, Kontadakis GA, Yoo S, *et al*. Transepithelial phototherapeutic keratectomy using a 213-nm solid-state laser system followed by corneal collagen cross-linking with riboflavin and UVA irradiation? *J Ophthalmol* 2010; **2010**: 146543. doi: 10.1155/2010/146543.
17. Kymionis GD, Grentzelos MA, Kounis GA, Diakonis VF, Limnopoulou AN, Panagopoulou SI. Combined transepithelial phototherapeutic keratectomy and corneal collagen cross-linking for progressive keratoconus. *Ophthalmol* 2012; **119(9)**:1777-84. doi: 10.1016/j.ophtha.2012.03.038.
18. Sarac O, Kosekahya P, Caglayan M, Tanriverdi B, Taslipinar Uzel AG, Cagil N. Mechanical *versus* transepithelial phototherapeutic keratectomy epithelial removal followed by accelerated corneal crosslinking for pediatric keratoconus: Long-term results. *J Cataract Refract Surg* 2018; **44(7)**:827-35. doi: 10.1016/j.jcrs.2018.04.039.
19. Grentzelos MA, Liakopoulos DA, Siganos CS, Tsilimbaris MK, Pallikaris IG, Kymionis GD. Long-term comparison of combined t-PTK and CXL (cretan protocol) *versus* CXL with mechanical epithelial debridement for keratoconus. *J Refract Surg* 2019; **35(10)**:650-5. doi: 10.3928/1081597X-20190917-01.
20. Kymionis GD, Grentzelos MA, Kankariya VP, Liakopoulos DA, Karavitaki AE, Portaliou DM, *et al*. Long-term results of combined transepithelial phototherapeutic keratectomy and corneal collagen crosslinking for keratoconus: Cretan protocol. *J Cataract Refract Surg* 2014; **40(9)**:1439-45. doi: 10.1016/j.jcrs.2014.01.040.
21. Gaster RN, Ben Margines J, Gaster DN, Li X, Rabinowitz YS. Comparison of the effect of epithelial removal by transepithelial phototherapeutic keratectomy or manual debridement on cross-linking procedures for progressive keratoconus. *J Refract Surg* 2016; **32(10)**:699-704. doi: 10.3928/1081597X-20160712-01.
22. Shakir M, Rameez F, Zafar S, Sulaiman MA. Initial experience of corneal collagen cross linking in progressive keratoconus. *Pak J Ophthalmol* 2018; **34(2)**.
23. Ozdas D, Yesilirmak N, Sarac O, Cagil N. 36-month outcomes of mechanical and transepithelial PTK epithelium removal techniques prior to accelerated CXL for progressive keratoconus. *J Refract Surg* 2022; **38(3)**: 191-200. doi: 10.3928/1081597X-20220114-03.