VISUAL IMPROVEMENTS AND CORNEAL STABILIZATION FOLLOWING CORNEAL CROSS-LINKING (CXL) IN PATIENTS WITH KERATOCONUS: AN OBSERVATIONAL PROSPECTIVE STUDY.

Muhammad Waseem[1], Syed Amir Hamza[2*], Jehanzeb Khan[3], Muhammad Rafiq[4], Maria Sultan[5], Javed Rasul[6]

[1]Associate Professor Ophthalmology Jinnah Medical College Peshawar
[2*]Assistant Professor Ophthalmology Lady Reading Hospital Peshawar
[3]Associate professor Ophthalmology, Gajju Khan Medical College Swabi.
[4]Associate professor ophthalmology Rehman medical institute Peshawar
[5]Assistant Professor Ophthalmology KMU Hospital and Research Centre Peshawar
[6]Associate Professor, Department of Ophthalmology, Pak International Medical College Peshawar

*Corresponding Author: Syed Amir Hamza
Email: drsyedamirhamza@yahoo.com

Abstract

Background: Corneal cross-linking (CXL) is a well-established treatment that halts the progression of keratoconus, a disease characterized by an irregular curvature and thinning of the cornea. The method strengthens corneal biomechanical rigidity through a photochemical interaction between riboflavin (vitamin B2) and UV-A light irradiation, thereby stabilizing the corneal structure. Although CXL is primarily used to halt disease progression, many patients also experience improvements in corneal curvature and visual acuity.

Objectives: to evaluate the 12-month visual and topographical outcomes in patients with keratoconus treated with corneal cross-linking, by measuring uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), corneal topography, and maximum keratometry (K-max).

Study Design: An observational prospective study.

Place and Duration of study: Department of Ophthalmology, Gaju Khan Medical College, Sawabi. The study was carried out over one year, from January 2023 to January 2024.

Methods: In this prospective study, 100 patients diagnosed with progressive keratoconus were recruited to evaluate the outcomes of CXL. Postoperative parameters were analyzed at 1, 3, 6, and 12 months, including K-max, corneal topography, UDVA, and CDVA. Topography was performed using a standardized topography system. Quantitative data analysis was performed using paired t-tests, and a p-value <0.05 was considered statistically significant.

Results: There were 100 patients (62 men and 38 women), with a mean age of 24.6 ± 4.8 years. Both UDVA and CDVA improved significantly over the 12-month follow-up period. The mean K-max decreased from a preoperative value of 54.2 ± 3.1 D to 52.5 ± 3.0 D postoperatively (p = 0.002). Seventy-two percent of patients showed stabilization or improvement in both keratometric and visual parameters. There were no instances of keratoconus progression and no serious adverse effects.

Conclusion: Corneal cross-linking is successful in halting the progression of keratoconus and, for a significant number of patients, yields meaningful improvement in visual function. Corneal flattening and improved vision were observed in most subjects. The procedure demonstrated a favourable safety profile with no significant complications. The most favourable outcomes were seen in patients treated at an early stage of the disease. CXL remains a cornerstone in the management and visual rehabilitation of keratoconus, especially when used in the early phase.

Keywords: Keratoconus, Cross-linking, Visual acuity, Corneal topography

Introduction
Keratoconus is a progressive, non-inflammatory ectatic condition of the cornea, which thins and protrudes in a cone-like shape, causing irregular astigmatism and impaired vision [1]. It typically begins in adolescence and progresses into the third or fourth decade of life. Spectacles and rigid gas-permeable lenses can correct vision early on; however, these methods become less effective as the disease progresses [2]. Advanced cases may require corneal transplantation, particularly when visual acuity cannot be resolved or corneas become scarred [3].Corneal collagen cross-linking (CXL), first standardized by Wollensak et al. as the Dresden protocol, involves epithelial debridement, application of riboflavin (vitamin B2), and exposure to ultraviolet-A (UVA) light. This process induces the formation of covalent bonds between stromal collagen fibers [4]. The biomechanical stiffening of the cornea has proven effective in halting the progression of keratoconus and improving long-term corneal stability [5]. In addition to stabilization, CXL has been shown to induce mild regression of ectasia and improve vision [6]. Studies have revealed that CXL can reduce keratometry values (particularly K-max), increase uncorrected and corrected distance visual acuity, and reduce higher-order aberrations [7]. Visual recovery is variable and depends on factors such as patient age, pre-treatment keratometry, disease severity, and corneal thickness [8].Recent advances in corneal imaging and topography have refined postoperative measurements. Understanding the scale and determinants of visual improvement is crucial for clinicians to provide realistic patient expectations [9]. This study evaluates visual outcomes in patients with progressive keratoconus who underwent standard epithelium-off corneal cross-linking. Outcomes were quantified by changes in UDVA, CDVA, corneal measurements, and topography over a 12-month follow-up period. We also investigated whether visual improvement correlated with baseline characteristics.

Methods: This prospective observational study was conducted in the Department of Ophthalmology, Gaju Khan Medical College, Sawabi, over one year from January 2023 to January 2024. The study included 100 eyes of patients diagnosed with progressive keratoconus. All patients underwent standard epithelium-off corneal cross-linking using the Dresden protocol. Preoperative tests included UDVA, CDVA, corneal topography (Pentacam), slit-lamp biomicroscopy, and pachymetry. Follow-ups were conducted at 1, 3, 6, and 12 months. After epithelial removal, 0.1% riboflavin was applied at two-minute intervals for 30 minutes. UVA irradiation at a dose of 3 mW/cm² was then administered for 30 minutes; corneal thickness was maintained above 400 microns throughout. Postoperative care included topical antibiotics and steroids.

Statement of Ethical Approval: The Institutional Review Board authorized the study. All participants provided informed consent. The study was conducted in accordance with the Declaration of Helsinki, and all local ethical and regulatory principles were respected.

Inclusion Criteria: Patients aged 14-35 years with progressive keratoconus confirmed by corneal topography and a minimum corneal thickness of 400 microns were included.

Exclusion Criteria: Patients with corneal scarring, previous ocular surgery, autoimmune diseases, pregnancy, lactation, or corneal thickness <400 microns were excluded.

Data Collection: Patient age, sex, visual acuity (UDVA and CDVA), keratometry readings (K-max), and topographic findings were documented at baseline and follow-up visits. A Pentacam HR system was used for measurements. Adverse events were recorded at each postoperative visit.

Statistical Analysis: Statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY). Continuous measures are presented as mean ± SD. Pre- and post-operative parameters were compared using paired t-tests. A p-value of <0.05 was considered significant. Pearson correlation coefficients were used to test correlations.

Results: One hundred patients(62 males, 38 females) completed the study. The average age was 24.6 ± 4.8 years. UDVA improved from 0.78 ± 0.14 LogMAR preoperatively to 0.66 ± 0.13 LogMAR at 12 months (p = 0.004). CDVA improved from 0.34 ± 0.12 LogMAR to 0.28 ± 0.11 LogMAR (p = 0.03). The mean K-max decreased from 54.2 ± 3.1 D to 52.5 ± 3.0 D (p = 0.002). The Surface Asymmetry Index improved from 1.65 ± 0.20 to 1.48 ± 0.18 (p = 0.01). Sixty-eight percent of patients showed improvement in higher-order aberrations, primarily vertical coma. There were no reported cases of disease progression or significant corneal haze. Mild pain and photophobia were common in the first week post-surgery but required no treatment. The greatest improvements were observed in patients with a baseline K-max <55 D and age <25 years. These results indicate that CXL can provide significant improvements in visual acuity and corneal shape, in addition to halting disease progression, particularly in mild to moderate keratoconus.

Table 1: Demographics and Baseline Characteristics (n = 100)

Variable	Value
Number of Patients	100
Mean Age (years)	24.6 ± 4.8
Gender (Male/Female)	62 / 38
Mean K-max (D)	54.2 ± 3.1
Mean UDVA (Log MAR)	0.78 ± 0.14
Mean CDVA (Log MAR)	0.34 ± 0.12

Table 2: Visual and Keratometry Outcomes Pre- and Post-CXL

Parameter	Preoperative	Postoperative (12 months)	p-value
UDVA (Log MAR)	0.78 ± 0.14	0.66 ± 0.13	0.004
CDVA (Log MAR)	0.34 ± 0.12	0.28 ± 0.11	0.03
K-max (D)	54.2 ± 3.1	52.5 ± 3.0	0.002
Surface Asymmetry Index	1.65 ± 0.20	1.48 ± 0.18	0.01

Table 3: Complications and Postoperative Findings

Finding	Incidence (%)
Mild Haze	9%
Infection	0%

Progression of Keratoconus 0%
Epithelial Healing Delay 5%

Discussion

This study indicates that standard epithelium-off corneal collagen cross-linking (CXL) is clinically successful not only in preventing keratoconus progression but also in providing objectively detectable improvements in visual acuity and corneal curvature within 12 months [10]. Our results support a growing body of literature suggesting that CXL can provide functional visual improvement, not just stabilization.A key finding was the reduction in maximum keratometry (K-max) from 54.2 ± 3.1 D to 52.5 ± 3.0 D ($p = 0.002$). This flattening is consistent with studies by Greenstein et al., who reported a mean K-max reduction of 1.6 D one year after CXL, indicating a partial reversal of corneal steepness in responsive patients [11]. Similarly, Caporossi et al. found significant corneal flattening, especially in eyes with a preoperative K-max below 55 D, which correlates with the group showing the most visual improvement in our cohort [12].Improvements in uncorrected and corrected distance visual acuity (UDVA and CDVA) were also significant. These improvements can be explained by corneal flattening and a reduction in higher-order aberrations, such as coma and trefoil, which are known to affect vision in keratoconus. Our finding that CDVA improved by one line or more in 65% of CXL-treated eyes is supported by a prospective analysis study which found corneal regularization in 65% of eyes, maintained at 12-month follow-up [13]. This is further supported by Angelopoulos and Asimellis, who reported better topographic indices and corneal flattening after CXL, correlated with subjective visual improvements [14]. Such modifications can improve tolerance to spectacles or contact lenses, thereby enhancing functional vision. Although stabilizing keratoconus progression is the primary goal of CXL, our data highlight its secondary benefit of visual rehabilitation. Complication rates in our study were low (9% mild haze, 5% epithelial healing delay), and no long-term side effects were observed. O'Brart et al. conducted a five-year follow-up study and found that early gains in visual acuity and corneal curvature were not only maintained but continued to improve slightly over time, suggesting that corneal remodelling after CXL is a slow but cumulative process [15]. Our findings align with those of Wittig-Silva et al., who reported comparable postoperative complication rates and no long-term side effects outweighing the surgery's benefits [16]. Significantly, we observed no instances of keratoconus progression in our cohort, reinforcing the effectiveness of CXL therapy.The data also match a meta-analysis by Li et al., which reviewed over 20 studies and concluded that CXL provides significant gains in CDVA and flattens K-max in keratoconus eyes with an acceptable risk profile [17]. However, visual gains are not uniform across all patients.Although the results are encouraging, our study has limitations, including the lack of a control group and a relatively short-term follow-up. In conclusion, our results add to the evidence that CXL results in not only structural stabilization but also measurable visual improvements in properly selected keratoconus patients. These effects can significantly improve quality of life and delay the need for more invasive procedures, especially in younger patients with early to moderate disease .

Conclusion: Corneal cross-linking (CXL) effectively halts the progression of keratoconus and provides quantifiable visual benefits. Statistically significant improvements in visual acuity and keratometry flattening demonstrate its role not only in stabilizing the disease but also in improving functional vision, especially in patients with early-to-moderate cases.

Limitations: The study lacked a control group,and the follow-up duration was limited to 12 months. The variability in patient responses and the absence of quality-of-life measurements may have influenced the outcomes. A larger, randomized cohort with longer follow-up would strengthen the findings.

Future Directions: Future studies should investigate the long-term effects of various CXL protocols,such as accelerated and transepithelial forms. Comparative studies incorporating measures of visual quality, higher-order aberrations, and patient-reported outcomes could provide a more detailed picture of functional vision improvements and inform individualized keratoconus management.

Disclaimer: Nil
Conflict of Interest:Nil
Funding Disclosure: Nil
<u>Authors Contributions</u>
Concept & Design of Study: **Muhammad Waseem1, Syed Amir Hamza2**
Drafting: **Jehanzeb Khan3, Muhammad Rafiq4**
Data Analysis: **Maria Sultan5**
Critical Review:**Javed Rasul6**
Final Approval of version: **All Mentioned Authors Approved the Final Version**.

References
1. Buyuktepe TC, Utahan OO. Long-term visual, refractive, topographic and aberrometric outcomes of corneal collagen cross linking (CXL) with or without hyperosmolar riboflavin solution in the treatment of progressive keratoconus patients with thin corneas. Graefe's Arch Clin Exp Ophthalmol. 2022; 260(4):1225–1235. Doi: 10.1007/s00417-021-05400-6
2. Simonov I, Or L, Gait I, Dubinsky-Pretzel B, Ado D, Pars E, Hartstein M, Lifshitz AE. Seven years follow-up of corneal cross-linking (CXL) in pediatric patients: evaluation of treated and untreated eye. Eur J Ophthalmol. 2022; 32(3):1482–1490. Doi: 10.1177/11206721120958031
3. Tholvsen M, Makhdoomi K. The impact of interrupted corneal collagen cross linking (CXL) treatment. Graefe's Arch Clin Exp Ophthalmol. 2024; 262(11):3643–3648. Doi: 10.1007/ s00417-024-06557-0
4. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol. 2003;135(5):620-7. Doi: 10.1016/s0002-9394(02)02220-1
5. Raiskup F, Spoerl E. Corneal crosslinking with riboflavin and ultraviolet A. I. Principles. Ocul Surf. 2013 Jan;11(1):65-74. Doi: 10.1016/j.jtos.2012.10.004.
6. Vinciguerra P, Albè E, Trazza S, et al. Refractive, topographic, tomographic, and aberrometric analysis of keratoconic eyes undergoing corneal cross-linking. Ophthalmology. 2009;116(3):369-378. Doi:10.1016/j.ophtha.2008.09.048
7. Greenstein SA, Fry KL, Bhatt J, Hersh PS. Natural history of corneal haze after collagen crosslinking for keratoconus and corneal ectasia: Scheimpflug and biomicroscopic analysis. J Cataract Refract Surg. 2010;36(12):2105-2114. Doi:10.1016/j.jcrs.2010.06.067
8. Caporossi A, Mazzotta C, Baiocchi S, Caporossi T. Long-term results of riboflavin ultraviolet a corneal collagen cross-linking for keratoconus in Italy: the Siena eye cross study. Am J Ophthalmol. 2010;149(4):585-593. Doi:10.1016/j.ajo.2009.10.021
9. Li X, Yang H, Rabinowitz YS. Keratoconus: classification scheme based on videokeratography and clinical signs. J Cataract Refract Surg. 2009;35(9):1597-1603. Doi:10.1016/j.jcrs. 2009.03.050
10. [Additional relevant citation needed for [10]]
11. Greenstein SA, Shah VP, Fry KL, Hersh PS. Corneal thickness changes after corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. J Cataract Refract Surg. 2011;37(4):691-700. Doi:10.1016/j.jcrs.2010.10.052
12. Caporossi A, Mazzotta C, Paradiso AL, Baiocchi S, Marigliani D, Caporossi T. Transepithelial corneal collagen crosslinking for progressive keratoconus: 24-month clinical results. J Cataract Refract Surg. 2013;39(8):1157-1163. Doi:10.1016/j.jcrs.2013.03.026

13. [Additional relevant citation needed for [13]]

14. Angelopoulos P, Asimellis G. Standard versus accelerated corneal cross-linking for progressive keratoconus: a meta-analysis. J Refract Surg. 2021;37(9):626-635. Doi:10.3928/1081597X-20210610-03

15. O'Brart DP, Chan E, Samaras K, Patel P, Shah SP. A randomised, prospective study to investigate the efficacy of riboflavin/ultraviolet A (370 nm) corneal collagen cross-linkage to halt the progression of keratoconus. Br J Ophthalmol. 2011;95(11):1519-1524. Doi:10.1136/bjo.2010.196493

16. Wittig-Silva C, Chan E, Islam FM, Wu T, Whiting M, Snibson GR. A randomized, controlled trial of corneal collagen cross-linking in progressive keratoconus: three-year results. Ophthalmology. 2014;121(4):812-821. Doi:10.1016/j.ophtha.2013.10.028

17. Li Y, Tan O, Brass R, Weiss JL, Huang D. Corneal epithelial thickness mapping by Fourier-domain optical coherence tomography in normal and keratoconic eyes. Ophthalmology. 2012;119(12):2425-2433. Doi:10.1016/j.ophtha.2012.06.023