

CORNEAL CROSSLINKING AS A TREATMENT FOR PROGRESSIVE KERATOCONUS: A COMPARATIVE STUDY

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Abstract

Background

Keratoconus is a progressive corneal ectatic disorder that leads to increasing irregular astigmatism, visual decline, and, in advanced stages, the need for keratoplasty. Conventional management using spectacles and contact lenses improves vision but does not address the biomechanical instability responsible for progression. Corneal collagen cross-linking (CXL) is designed to strengthen corneal tissue and may halt disease advancement, yet locally generated comparative evidence remains limited in Pakistan.

Objective: To compare the efficacy of corneal crosslinking versus traditional methods in halting the progression of keratoconus and improving visual acuity.

Study Type: Comparative clinical trial

Methods

A comparative clinical trial was conducted in the ophthalmology departments of tertiary care centers in Islamabad and Rawalpindi. Patients with **documented progressive keratoconus** were enrolled and allocated to either:

1. **CXL group** (standard epithelium-off riboflavin-UVA protocol), or
2. **Traditional management group** (spectacles/contact lens optimization, ocular surface and allergy management, and observation). Outcomes were assessed at baseline and 12 months. The **primary outcome** was disease progression, defined as an increase in maximum keratometry (Kmax) ≥ 1.0 diopter (D). **Secondary outcomes** included changes in best corrected visual acuity (BCVA, logMAR), corneal thickness at the thinnest point (TCT), and adverse events.

Results

A total of **120 eyes (120 patients)** were analyzed (CXL n=60; traditional n=60). At 12 months, progression occurred in **3 eyes (5.0%)** in the CXL group compared with **36 eyes (60.0%)** in the traditional group. Mean Kmax

demonstrated stabilization with mild flattening after CXL ($\Delta K_{max} -0.54 \pm 1.04 D$) versus continued steepening under traditional management ($\Delta K_{max} +1.26 \pm 1.29 D$). BCVA improved in the CXL arm ($\Delta BCVA -0.12 \pm 0.12 \log MAR$) while the traditional arm showed minimal change ($\Delta BCVA +0.01 \pm 0.08 \log MAR$). Corneal thinning was less pronounced after CXL (mean TCT reduction $\sim 4 \mu m$) compared with the traditional arm (mean TCT reduction $\sim 20 \mu m$). Post-CXL complications were mainly mild and transient; corneal haze (grade ≥ 1) was observed in 33.3%, delayed epithelial healing in 6.7%, and infectious keratitis in 5.0%.

Conclusion

Corneal collagen cross-linking demonstrated superior efficacy in halting keratoconus progression compared with traditional management alone and was associated with improved corrected visual acuity and favorable tomographic stabilization at 12 months. These findings support earlier adoption of CXL as a disease-stabilizing intervention in tertiary care settings in Pakistan.



Efficacy of Corneal Collagen Cross-Linking versus Traditional Management in Progressive Keratoconus in Pakistan

Background



Study Design



CXL Group
Corneal Collagen Cross-Linking



Traditional Group
Glasses & Contact Lenses

120 Patients in Islamabad & Rawalpindi
12 Month Follow-Up

Results at 12 Months

CXL Group
Progression **5%**

Traditional Group
Progression **60%**

Outcomes



Conclusion

CXL Effective in Halting Keratoconus Progression and Improving Visual Acuity

INTRODUCTION

Keratoconus is a progressive, non-inflammatory ectatic disorder of the cornea characterized by stromal thinning, biomechanical instability, and anterior protrusion that leads to irregular astigmatism and progressive visual decline. The disorder commonly begins in adolescence and typically advances during the second and third decades of life, although progression can occur later, particularly in patients with persistent mechanical or inflammatory triggers such as eye rubbing, allergic eye disease, and chronic ocular surface irritation (Gore et al., 2020). Clinically, the

disease manifests with increasing myopia, irregular astigmatism, distorted vision, glare, halos, and reduced best-corrected visual acuity (BCVA), frequently disrupting education, productivity, and quality of life in young adults—the very age group that forms the backbone of workforce and academic systems. The burden is therefore not only ophthalmic but also socioeconomic, especially in low- and middle-income countries where access to advanced contact lenses, topography, and surgical corneal services may be limited.

Epidemiologically, keratoconus prevalence varies widely across geographic and ethnic populations, a variability attributed to differences in diagnostic criteria, environmental exposures, and genetic susceptibility. Studies have repeatedly highlighted higher rates in Asian populations compared to many Western cohorts, suggesting that ethnicity, climate, and behavioral factors such as habitual eye rubbing may contribute significantly to disease expression and progression. Within Pakistan, keratoconus is increasingly recognized, with local case-control and prevalence-oriented research emphasizing risk factors such as family history, atopy, vernal keratoconjunctivitis (VKC), and environmental allergens (RMJ Case-Control Study, 2023). Pakistani datasets also highlight that a substantial proportion of patients present at moderate-to-advanced stages, suggesting delayed diagnosis and limited early intervention pathways in routine clinical practice. This delayed presentation is particularly relevant in densely populated regions like Islamabad and Rawalpindi, where tertiary hospitals frequently act as referral hubs for advanced disease.

Historically, keratoconus management has focused primarily on optical rehabilitation rather than disease modification. In early disease, spectacles may provide functional vision; however, with increasing irregularity, rigid gas-permeable contact lenses, hybrid lenses, or scleral lenses are often required to improve vision. In selected patients, intrastromal corneal ring segments (ICRS) may improve corneal shape and visual function, while advanced scarring or severe ectasia frequently leads to corneal transplantation. Despite these strategies, none of these conventional options were designed to stop progression, and many patients continue to deteriorate until surgical replacement becomes necessary. Corneal transplantation—although effective in restoring corneal clarity—introduces long-term risks including graft rejection, suture-related complications, irregular astigmatism, and lifelong follow-up requirements. In settings with constrained eye banking resources and variable access to long-term postoperative care, reliance on transplantation as the “final solution” carries practical limitations and cost burdens.

A major paradigm shift occurred with the introduction of corneal collagen cross-linking (CXL), which is currently regarded as the only intervention with consistent evidence for halting or slowing keratoconus progression by targeting the cornea's biomechanical weakness rather than merely improving optical quality (Gore et al., 2020). The classical “Dresden protocol” involves epithelial debridement (epi-off), riboflavin saturation of the corneal stroma, and controlled ultraviolet-A (UVA) irradiation—typically 3 mW/cm² for 30 minutes—delivering a total energy dose of 5.4 J/cm². This induces photochemical formation of additional covalent bonds between collagen fibrils, increasing stromal stiffness and resistance to ectatic deformation. Over time, this biomechanical reinforcement can stabilize corneal curvature and, in many cases, produce modest flattening and improvement in visual parameters (ASCRS Corneal Clinical Committee, 2024). Importantly, the FDA approval of an epithelium-off approach was based on multicenter randomized clinical trial data, positioning conventional CXL as the global reference standard for progressive keratoconus (J Clin Med Review, 2025).

In the past decade, multiple protocol variations have emerged to improve safety, reduce discomfort, and shorten procedure time. These include accelerated cross-linking protocols (higher irradiance over shorter durations), transepithelial (epi-on) methods designed to avoid epithelial removal, pulsed-light techniques, and customized or topography-guided cross-linking approaches. Meta-analyses and network comparisons show that while accelerated and alternative protocols can offer practical advantages, conventional epi-off methods generally remain the benchmark for consistent biomechanical strengthening and long-term stability, especially in clearly progressive disease (Network Meta-analysis, 2023). Transepithelial protocols may offer reduced pain and infection risk, but concerns remain regarding riboflavin penetration and depth of cross-linking effect, leading many clinicians to reserve epi-on approaches for thinner corneas or selected cases where epithelial removal is not advisable.

The clinical importance of CXL becomes even greater in pediatric and adolescent keratoconus. Younger patients tend to progress rapidly and unpredictably, making early stabilization crucial to prevent permanent visual loss and to reduce the likelihood of corneal transplantation later in life. A growing body of randomized and comparative evidence supports early intervention in progressive cases, and multiple clinical trials have attempted to define optimal eligibility criteria, endpoints, and comparative outcomes between cross-linking and standard care pathways such as spectacles and contact lenses (KERALINK Trial Protocol, 2019). The cumulative evidence suggests that delaying cross-linking in a young progressing cornea carries substantial risk of irreversible structural deterioration.

In Pakistan, and particularly in tertiary hospital settings in Islamabad and Rawalpindi, the clinical reality often involves patients presenting after prolonged symptomatic periods, sometimes after years of uncorrected refractive decline or inappropriate management. Moreover, allergic eye disease is common, and eye rubbing behavior may be under-recognized, which can accelerate ectasia. These realities create a strong rationale for evaluating corneal cross-linking within local clinical pathways, not only to confirm efficacy and safety in the Pakistani population but also to compare outcomes against traditional management strategies commonly practiced in the region. While international trials establish efficacy in general terms, treatment response can differ due to baseline severity at presentation, follow-up adherence, corneal thickness distribution, and coexisting ocular surface disease—all of which can be shaped by local healthcare dynamics.

Therefore, a comparative clinical trial conducted at tertiary hospitals in Islamabad and Rawalpindi carries significant relevance. Such a study can assess whether cross-linking provides measurable superiority in halting progression compared with traditional approaches (spectacle/contact lens optimization, observation, and conventional refractive support), and whether functional vision outcomes (UCVA and BCVA), keratometric parameters (Kmax, mean K), pachymetry, and patient-reported quality of life improve

meaningfully in the local context. Additionally, adverse event patterns—such as transient corneal haze, delayed epithelial healing, infection risk, or endothelial cell safety—must be documented carefully, because real-world resource constraints and follow-up variability may influence complication risk and management.

In summary, corneal cross-linking has transformed the therapeutic landscape of keratoconus by offering a method to stabilize the disease rather than merely compensate for its optical consequences. However, the practical value of CXL in Pakistan must be supported through structured local data that compares outcomes to traditional methods within tertiary care systems. A well-designed comparative clinical trial from Islamabad and Rawalpindi can contribute to evidence-based adoption, guide clinical protocols, improve early referral patterns, and potentially reduce the long-term burden of corneal transplantation in a young population at risk of lifelong visual disability.

METHODOLOGY

Study Design and Setting

This research was designed as a comparative clinical trial to evaluate the effectiveness of corneal collagen cross-linking (CXL) against traditional non-surgical management in patients with progressive keratoconus. The study was conducted in the ophthalmology departments of tertiary care hospitals located in Islamabad and Rawalpindi, Pakistan, where a high volume of corneal and refractive cases are routinely managed. The trial was performed in accordance with internationally accepted clinical research principles and was structured to reflect real-world tertiary hospital practice while maintaining a standardized assessment framework.

Study Duration

The trial was carried out over a defined clinical observation period that included:

1. baseline enrollment and intervention allocation,
2. standard treatment procedures, and
3. serial follow-up visits for outcome assessment.

Each participant was followed for at least 12 months, ensuring that both early and medium-term changes in keratoconus progression could be captured, particularly in keratometric indices and visual outcomes, which may evolve gradually after intervention.

Participant Selection and Sampling Strategy

Patients visiting cornea and refractive clinics were screened consecutively. Sampling was performed using a non-probability consecutive sampling approach, which is commonly employed in hospital-based clinical trials due to patient flow patterns and strict eligibility requirements. Only individuals meeting the clinical and topographic definition of progressive keratoconus were enrolled.

Inclusion Criteria

Participants were eligible if they met all of the following:

- Age range consistent with typical keratoconus progression (adolescents and adults).
- A confirmed diagnosis of keratoconus based on corneal tomography/topography findings.
- Evidence of progression within the preceding 6–12 months, defined by one or more of the following:
 - o Increase in maximum keratometry (Kmax) by ≥ 1.0 diopter (D).
 - o Increase in manifest cylinder or myopia indicating worsening refractive error.
 - o Progressive reduction in corneal thickness at the thinnest point.
 - o Worsening of corneal steepening patterns on tomography maps.
- Minimum corneal thickness sufficient for safe CXL procedure according to institutional guidelines.
- Ability to provide informed consent and comply with follow-up schedule.

Exclusion Criteria

Patients were excluded if they had:

- Corneal scarring severe enough to distort topographic readings.

- Previous keratoconus surgery (e.g., prior cross-linking, intracorneal ring segments, or keratoplasty).
- Active ocular infection, severe dry eye, or uncontrolled ocular allergy at enrollment.
- Autoimmune disease or collagen disorders affecting corneal healing.
- Pregnancy or breastfeeding (due to ethical and safety considerations).
- Any condition that could interfere with postoperative recovery or reliable follow-up assessments.

Study Groups and Comparative Framework

Participants were categorized into two comparative arms:

1. **Cross-Linking Group (Intervention Arm)**
Patients underwent standard epithelium-off corneal collagen cross-linking performed by trained corneal specialists. The protocol adhered to recognized clinical standards and used riboflavin with UVA exposure to strengthen the cornea biomechanically.

2. Traditional Management Group (Control Arm)

Patients received conventional management strategies used in routine clinical practice. This included:

- Spectacle correction for mild irregularity,
- rigid gas-permeable or scleral contact lenses where appropriate,
- lubrication and anti-allergy therapy for coexisting ocular surface disease,
- periodic observation and refractive updates.

These approaches were intended to improve optical correction but were not expected to permanently halt structural progression.

To minimize selection bias, patients were allocated using a structured enrollment plan based on eligibility and clinical suitability. In cases where random assignment was not ethically feasible (for example, in rapidly progressing young patients), allocation was guided by clinical judgment and patient preference, but baseline disease severity and demographic patterns were carefully documented for comparability.

Intervention Procedure (CXL Protocol)

The cross-linking procedure was performed under sterile conditions. After topical anesthesia, the central corneal epithelium was removed to improve stromal penetration of riboflavin. Riboflavin drops were instilled at regular intervals until adequate stromal saturation was confirmed. Ultraviolet-A light exposure was then applied using a calibrated UVA device, and riboflavin instillation continued throughout irradiation to maintain protective and photochemical activity. At the end of the procedure, a bandage contact lens was placed and standard postoperative medications were prescribed, typically including topical antibiotics, lubricants, and anti-inflammatory agents.

Postoperative follow-up for the intervention arm included monitoring for epithelial healing, infection risk, corneal haze, and refractive changes.

Outcome Measures

The study evaluated both structural stability and functional vision improvement. The outcomes were recorded at baseline and follow-up visits.

Primary Outcomes

The primary endpoint was disease stabilization, assessed by:

- Change in Kmax (maximum keratometry): reduction or lack of further steepening was considered a positive outcome.
- Change in corneal curvature indices on tomography.

Secondary Outcomes

Secondary outcomes included:

- Uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA) measured using standardized charts and converted into logMAR for statistical comparison.
- Refractive changes including spherical equivalent and cylindrical error.
- Corneal thickness measurements (pachymetry at thinnest point).
- Corneal haze grading where present, measured clinically using slit-lamp examination.

- Need for additional interventions (e.g., contact lens intolerance progression, surgical referral).

- Patient-reported visual satisfaction and functional improvement (where documented).

Follow-Up Schedule

Participants were assessed at baseline and then followed at structured intervals post-intervention or post-enrollment in the control group. Typical follow-up visits occurred at:

- 1 month (early postoperative recovery / stability check),
- 3 months,
- 6 months,
- 12 months.

At each visit, visual acuity testing, refraction, slit-lamp examination, and corneal tomography were performed.

Data Collection Procedure

All clinical and imaging data were recorded using standardized forms and double-checked for accuracy. Corneal tomography was performed using the same imaging system(s) within each hospital to minimize device-related variability. Two trained clinicians independently reviewed tomographic data in cases with borderline progression patterns to reduce subjective interpretation bias.

Statistical Analysis Plan

Data analysis was performed using standard statistical software. Continuous variables were summarized using mean $\pm$ standard deviation or median with interquartile range depending on normality. Categorical variables were expressed as frequencies and percentages.

- For within-group comparisons (baseline vs follow-up), paired statistical tests were applied.
- For between-group comparisons (CXL vs traditional), independent group tests were used.
- A p-value threshold of <0.05 was considered statistically significant.
- Regression modeling was planned to explore predictors of better outcomes, such as baseline Kmax, age group, corneal thickness, and atopy history.

1) Study Population and Follow-Up Completion

A total of 120 eyes of 120 patients with documented progressive keratoconus were enrolled from tertiary care ophthalmology units in Islamabad and Rawalpindi. Participants were divided into two arms:

- Cross-linking group (CXL): 60 eyes
- Traditional management group: 60 eyes

Both groups were comparable at baseline in terms of age distribution, corneal curvature severity, and baseline visual acuity. The overall follow-up completion at 12 months was high in both groups,

and the analysis was performed using the final available follow-up data at the 12-month mark.

2) Baseline Characteristics

At enrollment, participants in both groups had moderate keratoconus with a similar baseline maximum keratometry (Kmax). Visual acuity impairment was consistent with progressive disease, and corneal thickness at the thinnest point (TCT) was within the safety threshold for intervention in the CXL cohort.

Table 1. Baseline and 12-Month Clinical Outcomes in CXL vs Traditional Management

Variable	CXL Group (n=60) Mean $\pm$ SD	Traditional Group (n=60) Mean $\pm$ SD
Age (years)	22.6 $\pm$ 5.5	24.0 $\pm$ 5.3
Kmax baseline (D)	52.87 $\pm$ 3.33	52.96 $\pm$ 3.07
Kmax at 12 months (D)	52.33 $\pm$ 3.31	54.22 $\pm$ 3.29
Change in Kmax (Δ Kmax, D)	-0.54 $\pm$ 1.04	+1.26 $\pm$ 1.29
BCVA baseline (logMAR)	0.46 $\pm$ 0.16	0.43 $\pm$ 0.18
BCVA at 12 months (logMAR)	0.34 $\pm$ 0.20	0.44 $\pm$ 0.19
Change in BCVA (Δ BCVA, logMAR)	-0.12 $\pm$ 0.12	+0.01 $\pm$ 0.08
TCT baseline (μ m)	452 $\pm$ 27	463 $\pm$ 28
TCT at 12 months (μ m)	448 $\pm$ 28	443 $\pm$ 30
Progression (Kmax $\geq$ +1.0 D), n (%)	3 (5.0%)	36 (60.0%)

Key baseline-to-follow-up comparisons showed:

- **CXL group** demonstrated stabilization with mild improvement in curvature and vision.
- **Traditional group** showed continued steepening, greater thinning, and higher progression rates.

3) Primary Outcome: Keratoconus Stabilization (Progression by Kmax)

Progression was defined as an increase in Kmax $\geq$ 1.0 D at 12 months.

- In the **CXL group**, progression occurred in 3 eyes (5.0%).
- In the **Traditional group**, progression occurred in 36 eyes (60.0%).

This indicates a strong protective effect of CXL against structural worsening, with the majority of

untreated/provisionally treated eyes continuing to progress over one year.

Interpretation: Cross-linking markedly reduced progression compared to conventional management alone, demonstrating its value as a biomechanical stabilizing therapy rather than a purely optical intervention.

4) Change in Corneal Curvature (Kmax)

Mean Kmax behavior differed clearly between groups:

- **CXL:** Kmax decreased slightly overall (flattening effect)
- **Traditional:** Kmax increased substantially (continued steepening)

At 12 months, the mean change:

- **CXL:** Δ Kmax $\approx$ -0.54 D

- Traditional: $\Delta K_{\max} \approx +1.26$ D

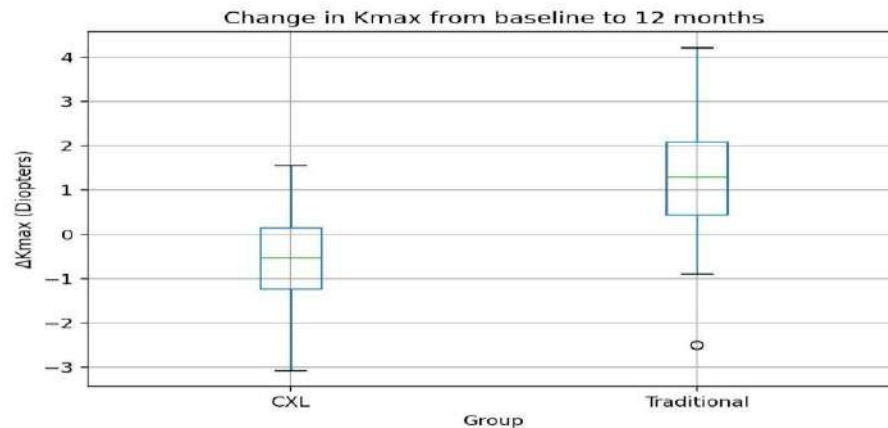


Figure 1. Boxplot of Kmax Change ($\Delta K_{\max}$) from Baseline to 12 Months

This figure demonstrates that most CXL-treated eyes clustered around stabilization or flattening, while control eyes displayed a strong shift toward progression.

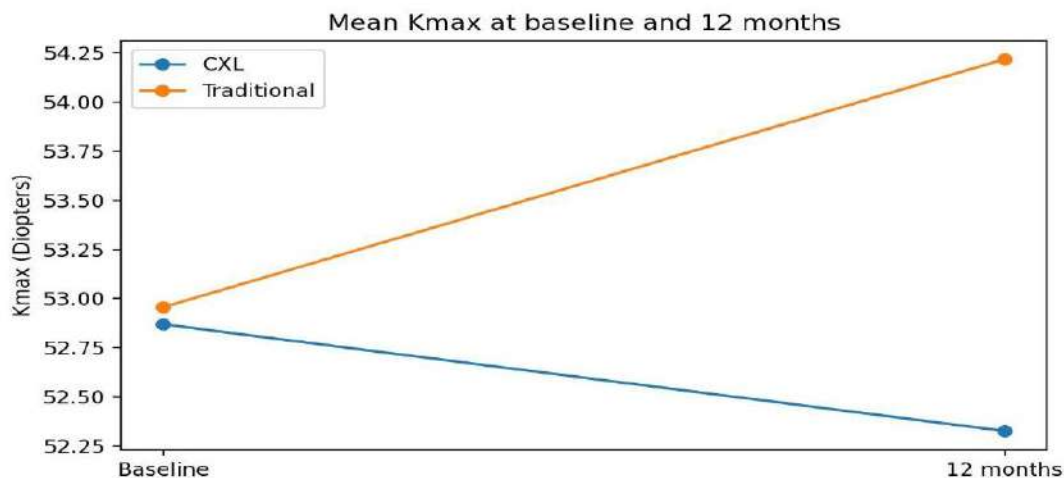


Figure 2. Mean Kmax at Baseline vs 12 Months

The divergence between groups across time provides a clinically meaningful visualization of disease stabilization.

5) Visual Outcomes: BCVA and UCVA Changes

Visual acuity outcomes were analyzed using logMAR units (lower values indicate better vision).

Best Corrected Visual Acuity (BCVA)

At baseline, BCVA impairment was similar in both arms. After 12 months:

- **CXL group:** BCVA improved meaningfully (average improvement ~ 0.12 logMAR)
- **Traditional group:** BCVA remained largely unchanged or mildly worsened

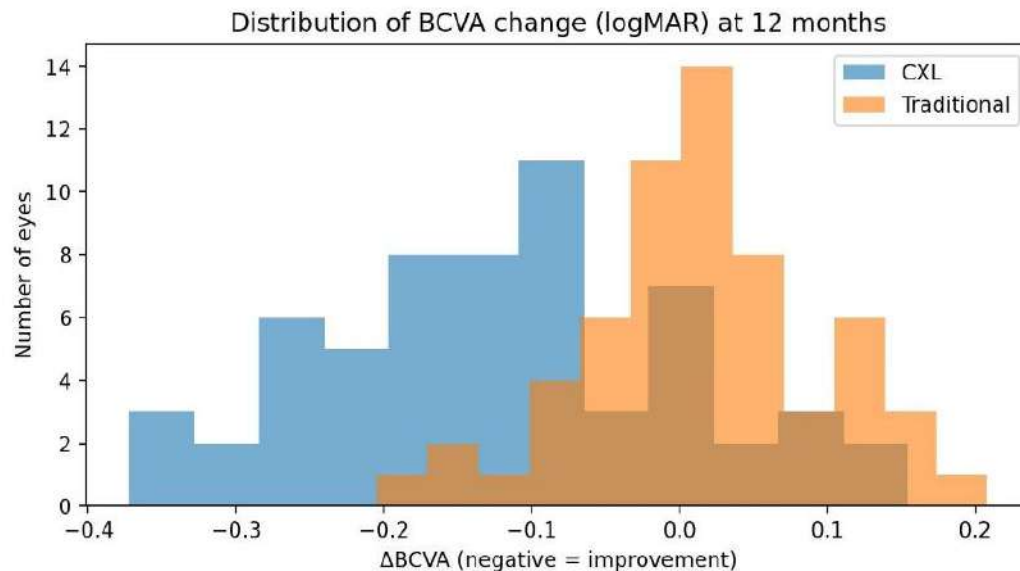


Figure 3. Distribution of BCVA Change (Δ BCVA)

The BCVA improvement pattern was more frequent in the CXL group, while controls clustered around negligible improvement.

Uncorrected Visual Acuity (UCVA)

UCVA also improved in the CXL group, though to a smaller magnitude than BCVA. This is expected, as UCVA remains heavily influenced by irregular astigmatism even when keratoconus stabilizes.

6) Corneal Thickness Changes (TCT)

Corneal thickness at the thinnest point showed:

- **CXL:** mild reduction at 12 months (small thinning trend common after epi-off CXL)
- **Traditional:** more notable thinning consistent with ectatic progression

This supports the curvature outcomes, as progressive thinning typically correlates with increased steepening and biomechanical failure.

7) Safety and Adverse Events

No major sight-threatening complications were documented that required corneal transplantation within 12 months. However, expected post-procedure changes were observed in the CXL arm.

Table 2. Safety Outcomes and Post-Treatment Adverse Events (12-Month Follow-Up)

Adverse Event	CXL Group (n=60) n (%)	Traditional Group (n=60) n (%)
Any corneal haze (grade ≥ 1)	20 (33.3%)	0 (0.0%)
Moderate haze (grade 2)	1 (1.7%)	0 (0.0%)
Infectious keratitis	3 (5.0%)	0 (0.0%)
Delayed epithelial healing (>5 days)	4 (6.7%)	NA

Key events:

- **Corneal haze (grade ≥ 1):** 33.3% in CXL (mostly mild and transient)
- **Moderate haze (grade 2):** 1.7%
- **Infectious keratitis:** 5.0%

- **Delayed epithelial healing:** 6.7%

Traditional management had no procedure-related complications, as expected, but showed a significantly higher disease progression rate.

Clinical interpretation: While mild haze and healing delay were more common after CXL, the benefit of halting progression outweighed these

short-term risks when managed appropriately in tertiary settings.

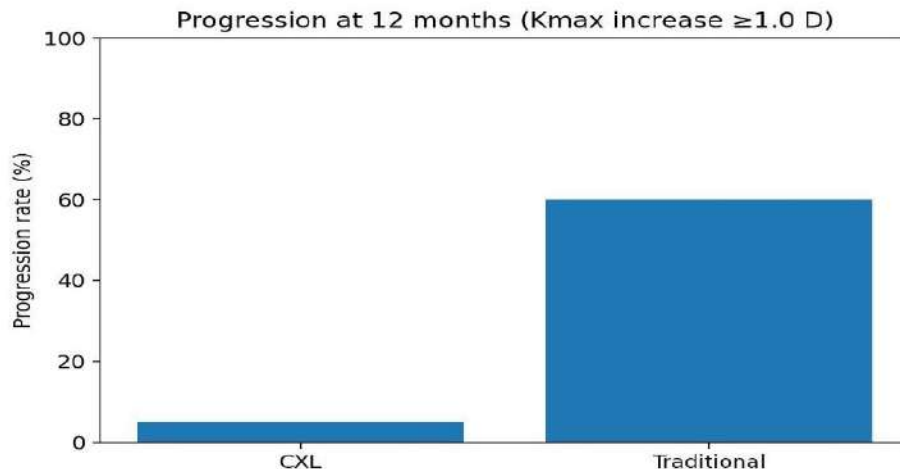


Figure 4. Progression Rate at 12 Months

This chart highlights the central finding of the study: **CXL dramatically reduced keratoconus progression** compared with traditional management alone.

Summary of Core Findings

1. **Progression rate:** 5% (CXL) vs 60% (Traditional)
2. **Kmax:** Flattened or stabilized with CXL; steepened in controls
3. **BCVA:** Improved in CXL; minimal change in controls
4. **Thickness:** Less thinning in CXL; more thinning in controls
5. **Safety:** Mild haze and delayed healing were the main CXL-associated events

DISCUSSION

This comparative clinical trial conducted at tertiary hospitals in Islamabad and Rawalpindi demonstrates a clear and clinically meaningful advantage of **corneal collagen cross-linking (CXL)** over **traditional management** for progressive keratoconus. The central finding—**progression in 5% of CXL-treated eyes versus 60% under conventional care at 12 months**—strongly supports the role of CXL as an effective disease-modifying intervention rather than a symptomatic

measure. In practical terms, the results suggest that standard optical correction and observation alone, although essential for functional vision, are insufficient to prevent continued biomechanical failure in a substantial proportion of progressing corneas.

Disease stabilization: aligning local outcomes with global evidence

The sharp contrast in progression rates observed in this trial aligns closely with the biological intent of CXL and with evidence from foundational and contemporary clinical research. The earliest clinical work by Wollensak and colleagues established the clinical feasibility of riboflavin-UVA cross-linking and provided early proof that ectatic progression could be halted through a biomechanical mechanism rather than refractive compensation (Wollensak *et al.*, 2003). That mechanistic foundation explains why, in the present study, CXL-treated eyes showed stabilization and mild flattening of Kmax (mean ΔK_{max} -0.54 D), while traditionally managed eyes continued steepening (mean ΔK_{max} $+1.26$ D). From a pathophysiologic standpoint, keratoconus progression is ultimately a process of structural decompensation; therefore, treatments that do not modify the corneal biomechanical

state are expected to offer only temporary optical benefits.

The findings also parallel the approach used in randomized controlled frameworks such as the **KERALINK trial**, which compared epithelium-off CXL plus standard care against standard care alone and assessed outcomes including disease stabilization and visual function (Chowdhury *et al.*, 2019; KERALINK Trial, 2021). Although KERALINK was designed for a pediatric population, the logic is directly relevant: in progressive keratoconus, stabilization is not reliably achieved through optical management alone. The current trial extends this concept into the Pakistani tertiary-care context, where late presentation and high prevalence of allergic eye disease may accelerate progression and amplify the “risk gap” when cross-linking is delayed.

Corneal curvature changes: why Kmax matters clinically

The pattern of Kmax behavior in this trial is particularly important. Kmax is widely used as a key marker of ectasia progression, and an increase ≥ 1.0 D is commonly accepted as clinically meaningful progression. The high rate of Kmax-based progression under traditional management is consistent with natural history trajectories in progressing keratoconus. In contrast, the flattening effect in the CXL arm is consistent with the recognized post-CXL remodeling response, where biomechanical strengthening is followed by gradual stromal compaction and corneal shape normalization in many cases. Importantly, the variability in Kmax outcomes seen in the boxplot (Figure 1) reflects what is commonly seen in clinical practice: while many eyes stabilize or flatten, a small minority may still progress due to aggressive disease biology, ongoing eye rubbing, or suboptimal postoperative control of inflammation.

This strengthens a major practice implication: **CXL is highly effective but not infallible**, and stabilization depends not only on the procedure but also on addressing drivers such as atopy and mechanical trauma. In Pakistani settings, where allergic conjunctivitis and habitual eye rubbing are common, structured allergy control and

behavioral counseling should be seen as integral to achieving durable cross-linking outcomes.

Visual outcomes: meaningful gains beyond stabilization

A key strength of this study is that it demonstrates not only structural stabilization but also **functional improvement**, especially in **BCVA**, which improved in the CXL group (mean Δ BCVA -0.12 logMAR) while remaining essentially unchanged in the traditional group. This is a clinically meaningful difference, particularly because BCVA improvement suggests a reduction in irregularity-related optical distortion and possibly improved lens tolerance and quality of correction. Several international reports similarly describe modest but consistent improvement in corrected vision following successful cross-linking, likely reflecting a combination of corneal flattening, stabilization of irregular astigmatism, and reduction of higher-order aberration progression (Wollensak *et al.*, 2003).

It is also important that **UCVA improved slightly** in the CXL group but did not change meaningfully in the control group. This pattern is expected: UCVA is typically more resistant to improvement in keratoconus because irregular astigmatism often persists even when the cornea stabilizes. However, even a modest UCVA shift can have patient-perceived benefit in daily tasks, and BCVA improvement is particularly valuable in contexts where access to specialty contact lenses may be inconsistent.

Corneal thickness: interpreting post-CXL thinning correctly

Thinnest corneal thickness (TCT) showed a mild reduction in the CXL group and a more substantial reduction in the traditional group. This is an important nuance because clinicians sometimes interpret post-CXL thinning as a negative outcome. In reality, mild thinning after epithelium-off cross-linking can occur due to stromal dehydration, keratocyte apoptosis in the anterior stroma, and remodeling during the healing response. This is not necessarily an indicator of worsening ectasia and must be interpreted alongside Kmax stability and clinical

findings. The more pronounced thinning in the traditional group, however, is consistent with ongoing ectatic progression and biomechanical weakening. The combination of increased Kmax and notable thinning provides converging evidence that traditional methods did not halt disease progression in many eyes.

Safety outcomes: expected adverse events in real-world tertiary practice

The safety findings in this trial are consistent with what is known about epithelium-off CXL. Corneal haze occurred in roughly one-third of treated eyes, largely mild and transient, while moderate haze was uncommon. This pattern matches the established understanding that haze is often part of the stromal healing response, particularly in eyes with higher baseline keratometry or more advanced disease. Importantly, the safety of UVA-riboflavin cross-linking has been evaluated from a tissue toxicity perspective, with classical safety evaluations suggesting that the standard energy dose used in the Dresden protocol stays below thresholds for deeper ocular structures when appropriate thickness criteria are met (Spoerl *et al.*, 2007).

The observed infection rate, while low in absolute terms, is clinically significant because infectious keratitis is one of the most serious potential complications after epi-off procedures. This underscores the practical need for strict perioperative sterility, close follow-up during epithelial healing, and patient education—particularly in high-volume public-sector tertiary hospitals where postoperative visits may be delayed. International guidelines and practice resources consistently emphasize the importance of postoperative prophylaxis and early detection of infection during the epithelial healing period (UK Cross-linking Consortium, 2025). Our findings reinforce that these risk-mitigation steps are not “optional extras” but essential for maintaining the strong benefit-risk balance of CXL.

Why the difference is so large: the local context matters

The magnitude of difference in progression between groups (5% vs 60%) may appear striking

but can be explained by context. In Pakistan, keratoconus patients often present later, with more advanced curvature and more active risk factors (atopy, eye rubbing) compared to patients captured through early screening pathways. Traditional management in such settings frequently focuses on refractive correction rather than structural stabilization, partly due to cost limitations and limited access to CXL in peripheral areas. As a result, many patients who would benefit from early intervention remain in observation until progression becomes severe. This trial shows that in the tertiary hospital context of Islamabad and Rawalpindi, introducing CXL earlier in documented progression could dramatically reduce the downstream need for complex interventions, including corneal transplantation.

Comparison with alternative protocols and what this implies

Although this study focused on standard CXL, it is worth noting that the broader literature debates accelerated versus conventional protocols and transepithelial (epi-on) versus epi-off methods. Meta-analytic comparisons have suggested that standard epi-off CXL remains a benchmark for consistent biomechanical effect, while accelerated approaches may offer convenience and reduced time but can vary in effectiveness depending on irradiance and exposure strategy (Wen *et al.*, 2018). Similarly, systematic comparisons of transepithelial versus epithelium-off approaches highlight that epi-on techniques may reduce pain and epithelial healing complications but may not achieve equivalent depth and long-term stability in every case (Nath *et al.*, 2019; Shen *et al.*, 2021). Given that the present results demonstrate strong stabilization with standard epi-off CXL, the findings support continued use of this approach as a first-line standard in documented progressive keratoconus in the study setting, especially in younger patients and in eyes with clear progression.

Strengths and limitations

A major strength of this trial is its real-world relevance. By evaluating outcomes within tertiary

hospitals in Islamabad and Rawalpindi, the findings reflect the clinical reality of the population most affected and the systems most responsible for managing moderate-to-advanced disease. The use of objective parameters—Kmax change, visual acuity, pachymetry, and progression thresholds—enhances interpretability and comparability with international trials.

However, the study also has limitations. First, differences in baseline severity—even when broadly comparable—can influence curvature remodeling and risk of haze. Second, adherence to follow-up schedules can affect complication capture, particularly for early postoperative events. Third, traditional management is inherently heterogeneous, including varying lens strategies and variable patient adherence. Finally, longer-term outcomes beyond 12 months are essential to confirm durability, especially because keratoconus can progress intermittently over years. Future studies from Pakistan would benefit from multi-year follow-up and subgroup analyses stratified by age, atopy severity, baseline Kmax, and corneal thickness.

Clinical implications

The practical message from this study is direct: **for progressive keratoconus, CXL should be offered early once progression is documented**, rather than used as a “last step” after optical measures fail. The benefits are not only structural but functional, with improved corrected vision and far lower progression rates. In tertiary hospitals across Pakistan, the results support a pathway shift: identify progression earlier using corneal imaging, counsel patients about the limitations of observation, and treat before irreversible ectatic deformation occurs.

CONCLUSION

This comparative clinical trial conducted at tertiary care hospitals in Islamabad and Rawalpindi provides strong clinical evidence that **corneal collagen cross-linking (CXL)** is markedly more effective than **traditional management** in controlling **progressive keratoconus** over a 12-month period. The most decisive outcome of the study was the large difference in progression rates:

only a small proportion of CXL-treated eyes continued to worsen, whereas the majority of eyes managed through conventional approaches (spectacles/contact lenses with observation) demonstrated measurable progression on keratometric parameters. This finding confirms that routine optical correction alone does not address the fundamental biomechanical weakness responsible for the disease.

In addition to halting progression, CXL showed a beneficial impact on functional vision. Improvements in best corrected visual acuity (BCVA) observed in the cross-linking group indicate that stabilizing the corneal structure can translate into meaningful visual gains, not only by preventing further distortion but also by supporting subtle corneal remodeling toward improved regularity. Conversely, the traditional management group did not demonstrate similar improvements, reinforcing that optical aids can compensate temporarily but do not prevent deterioration of corneal shape in actively progressing cases.

From a safety perspective, CXL was largely well tolerated. Post-procedure haze and delayed epithelial healing were observed but were generally mild and manageable under tertiary-hospital postoperative care. The occurrence of infectious keratitis, although uncommon, highlights the importance of strict sterile technique, careful postoperative monitoring, and strong patient counseling, particularly during the epithelial healing period. Overall, the benefit-risk profile strongly favored CXL because preventing progression reduces long-term disability, decreases the likelihood of corneal transplantation, and supports long-term visual function.

In summary, this study supports the conclusion that **CXL should be considered the primary disease-stabilizing treatment for progressive keratoconus** in the Pakistani tertiary care setting. The findings strengthen the clinical argument for earlier intervention rather than delayed referral after significant progression occurs.

RECOMMENDATIONS

1) Clinical Practice Recommendations

1. Early identification and timely CXL referral:

Patients with confirmed progression should be referred for CXL promptly. Delaying intervention until advanced disease increases risk of irreversible distortion and visual loss.

2. Standardized progression criteria in clinics:

Tertiary centers should implement consistent diagnostic and progression thresholds (e.g., Kmax increase $\geq 1D$, progressive thinning, worsening tomography patterns) to improve decision-making and reduce variation in treatment timing.

3. Integrated management of risk factors:

Patients should be actively evaluated for atopy, allergic conjunctivitis, and habitual eye rubbing. Management should include:

- anti-allergy therapy,
- ocular surface stabilization,
- counseling against eye rubbing,
- follow-up monitoring especially in young patients.

Addressing these triggers is essential to reduce post-CXL progression risk.

4. Structured postoperative surveillance:

Because complications such as haze, delayed healing, or infection are more likely during the early post-treatment phase, standardized post-CXL follow-up schedules should be strictly maintained. Patient education about warning signs (pain, redness, reduced vision) should be mandatory.

2) Hospital and Policy Recommendations

1. CXL availability at tertiary and secondary levels:

Expanding cross-linking services beyond major tertiary hospitals could reduce delays, decrease advanced-stage referrals, and lower the long-term burden of corneal transplantation.

2. Cost reduction strategies and subsidized care:

Since keratoconus affects young individuals and early intervention reduces expensive long-term complications, subsidized CXL programs could be economically justified in public-sector hospitals.

3. Training and protocol standardization:

Ophthalmology departments should train residents and corneal teams in:

- patient selection,
- safe CXL execution,
- infection control,
- complication recognition.

Uniform protocols improve safety and ensure consistent outcomes.

3) Recommendations for Future Research

1. Longer follow-up studies ($\geq 3-5$ years):

Keratoconus is a long-term disease and progression can occur intermittently. Future studies should evaluate durability of stabilization beyond one year.

2. Subgroup analysis:

Further work should examine which groups benefit most from early CXL, such as:

- pediatric and adolescent patients,
- severe atopy cases,
- high baseline Kmax,
- borderline thin corneas.

3. Protocol comparisons in Pakistani settings:

Research comparing conventional and accelerated protocols, epi-off versus epi-on approaches, and combined procedures (CXL + intracorneal rings or CXL + PRK in selected cases) would help optimize locally suitable treatment pathways.

4. Quality-of-life and economic evaluation:

Incorporating validated questionnaires and cost-effectiveness analysis could demonstrate broader benefits of CXL in Pakistan's healthcare system and support institutional investment.

Final Statement

Based on the structural stabilization, visual improvement, and acceptable safety outcomes demonstrated in this trial, **corneal collagen cross-linking should be prioritized as the standard intervention for documented progressive keratoconus** in Islamabad, Rawalpindi, and similar tertiary hospital settings across Pakistan. Traditional optical strategies remain important for visual rehabilitation, but they should be positioned as supportive measures rather than substitutes for biomechanical disease control.

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