Original Article

Macular safety and outcomes of accelerated cross-linking with a 7.2 J/cm² energy dose in keratoconus: A prospective case series

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Abstract:

PURPOSE: The purpose of this study was to evaluate the macular safety and clinical outcomes of an accelerated Corneal collagen crosslinking (CXL) protocol using 12 mW/cm² ultraviolet-A (UV-A) irradiation for 10 min (total energy dose: 7.2 J/cm²) with dextran-free riboflavin, assessing its efficacy and posterior segment safety in patients with progressive keratoconus.

METHODS: Seventeen eyes of 17 patients with progressive keratoconus underwent accelerated epithelium-off CXL using 12 mW/cm² UV-A irradiation for 10 min (total energy: 7.2 J/cm²). Dextran-free 0.1% riboflavin was instilled following epithelial debridement. Treatment proceeded only if corneal thickness was ≥400 μm. Pre- and 12-month postoperative assessments included best-corrected visual acuity (BCVA), corneal topography, endothelial cell count, multifocal electroretinography (mfERG), and enhanced depth imaging optical coherence tomography. Lens clarity was evaluated by slit-lamp biomicroscopy. The Wilcoxon signed–rank test was used for paired comparisons; $P < 0.05$ was considered statistically significant.

RESULTS: Although the median BCVA improved from 0.46 to 0.38 logarithm of the minimum angle of resolution, this change was not statistically significant ($P = 0.15$). mfERG analysis showed increased P1 wave amplitudes and decreased implicit times across most retinal rings; however, these changes were also not statistically significant. Choroidal vascular parameters remained stable without significant alterations. No adverse events or lenticular opacities were observed during the follow-up period.

CONCLUSION: The accelerated continuous CXL protocol delivering a total energy dose of 7.2 J/cm² demonstrated macular safety over 12 months, with no significant impact on choroidal vascular structure or retinal function. These findings support the safety and potential efficacy of this protocol in stabilizing progressive keratoconus and highlight the need for further long-term, controlled studies to validate its outcomes.

Keywords:

Accelerated CXL, choroidal vascularity index, keratoconus, macular safety, multifocal electroretinography

Introduction

Keratoconus is a progressive, asymmetric ectatic disorder of the cornea, characterized by stromal thinning, conical protrusion, and irregular astigmatism. It typically begins in adolescence or early adulthood, progressively impairing visual acuity and in advanced stages, may lead to corneal scarring or even blindness.[1-3] Beyond visual disability, keratoconus significantly compromises quality of life, affecting daily activities and causing emotional and psychological distress.[4]

Corneal collagen cross-linking (CXL) has emerged as the only available intervention capable of halting the progression of keratoconus. Since the introduction of the standard Dresden protocol entailing riboflavin administration followed by ultraviolet-A (UV-A) irradiation at 3 mW/cm² for 30 min, CXL has become the gold standard in disease stabilization.[5-9] However, the long treatment duration, risk of corneal dehydration, epithelial damage, and patient

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discomfort have prompted the development of accelerated protocols, which aim to deliver equivalent total energy in a shorter time by increasing UV-A intensity.[10,11]

Accelerated CXL protocols, based on the Bunsen–Roscoe law of reciprocity, have demonstrated comparable efficacy to conventional methods in stabilizing keratoconus. Nevertheless, concerns persist regarding the possible effects of higher UV-A intensities on posterior segment structures, particularly the macula and retina. Experimental and clinical studies have raised questions about potential phototoxic effects, including oxidative stress and subclinical retinal changes.[12-15]

The macula is essential for central vision, and its structural and functional integrity must be preserved following high-intensity CXL. Although the procedure is intended to target the cornea, energy transmission through ocular media may theoretically pose risks to deeper structures.[16-19] Advances in diagnostic technologies, such as enhanced depth imaging optical coherence tomography (EDI-OCT) and multifocal electroretinography (mfERG), now allow for a more detailed evaluation of macular structure and function, enabling researchers to address these concerns comprehensively.[20-22]

This study evaluates the macular safety and clinical efficacy of an accelerated continuous CXL protocol delivering a total energy dose of 7.2 J/cm² using dextran-free riboflavin in progressive keratoconus patients. By integrating advanced imaging modalities and electrophysiological assessments, this research seeks to provide a thorough analysis of macular safety while exploring the clinical outcomes of this novel protocol. These findings contribute to optimizing CXL protocols to enhance patient safety and treatment outcomes.

Methods

This prospective study was conducted at Ondokuz Mayıs University Faculty of Medicine, Department of Ophthalmology and included 17 eyes of 17 consecutive patients diagnosed with progressive keratoconus who underwent accelerated continuous cross-linking (CXL). Ethics approval was obtained from the Ondokuz Mayıs University Faculty of Medicine Ethics Committee (Decision number: OMÜ KAEK 2020/699) and the Turkish Medicines and Medical Devices Agency (Decision number: E-68869993-511.06-702286). The study adhered to the tenets of the Declaration of Helsinki, and written informed consent was obtained from all participants.

Patients were eligible if progressive keratoconus was confirmed by clinical examination, best-corrected visual acuity (BCVA), and corneal topography. Inclusion criteria included a minimum corneal thickness of 350 μm at the thinnest point, a clear cornea, and the absence of other ocular pathologies. Patients were excluded if they had a history of herpetic keratitis, corneal scarring, retinal or optic nerve pathologies, prior ophthalmic surgery, severe dry eye, systemic conditions affecting the eye, pregnancy or breastfeeding, or if they were under 18 years of age.

Preoperative evaluations were performed 3 days before surgery, and follow-up assessments were conducted at 12 months. BCVA was measured using a logarithm of the minimum angle of resolution (logMAR) chart. Corneal topographic indices, including mean keratometry (Km), maximum keratometry (Kmax), keratoconus index (KI), and central KI (CKI), were obtained using the Pentacam HR (Scheimpflug camera, Oculus Inc., Wetzlar, Germany). Central and thinnest corneal thicknesses (CCT and TCTs) were also documented. Endothelial cell density was measured through specular microscopy.

Choroidal vascular parameters, including luminal area (LA), total choroidal area (TCA), and choroidal vascularity index (CVI), were assessed using EDI-OCT (Spectralis OCT, Heidelberg Engineering GmbH, Germany) and analyzed with ImageJ software (National Institutes of Health, Bethesda, MD, USA).

The macular function was evaluated using mfERG performed with the Metrovision MonPack One system (Metrovision, Perenchies, France). The mfERG analysis included P1 wave amplitudes and implicit times recorded across five concentric retinal rings:

- Ring 1 (Fovea, <2° ~1500 μm central)
- Ring 2 (Parafovea, 2–5° ~2500 μm)
- Ring 3 (Perifovea, 5–10° ~5500 μm)
- Ring 4 (Outer Macula, 10–15°)
- Ring 5 (Outermost Macula, >15°).

Each recording lasted approximately 5 min per eye, with 5004 stimuli presented per test. Patients maintained foveolar fixation with a monitoring camera to ensure accuracy.

The CXL procedure was performed by a single surgeon (E. C.) using the Avedro KXL system (Avedro Inc., Waltham, MA, USA) with a UV-A irradiance of 12 mW/cm² for 10 min, delivering a total energy dose of 7.2 J/cm². Topical anesthesia was administered with 0.5% proparacaine HCl drops (Alcaine, Alcon Laboratories, Fort Worth, TX, USA). The central corneal epithelium was debrided using 20% alcohol applied within an 8-mm ring marker for 30 s. Riboflavin solution (VibeX Rapid, Avedro Inc.), containing 0.1% riboflavin and 1.1% hydroxypropyl methylcellulose (dextran-free), was instilled every 30–60 s for 10 min before continuous UV-A irradiation. Riboflavin application was continued every minute throughout the procedure. At the end of treatment, the cornea was irrigated with 0.9% saline, 5% moxifloxacin drops (Moxai, Abdi İbrahim Pharmaceuticals, Turkey) were applied, and a bandage contact lens was placed.

Postoperative care included moxifloxacin 0.5% eye drops administered four times daily for 1 week, dexamethasone 0.1% eye drops tapered over 4 weeks, and sodium hyaluronate 0.15% eye drops (Eyestil, Sifi S. p. A, Italy) applied four times daily for 1 month. The bandage contact lens was removed during the first postoperative week.

Statistical analyses were performed using SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA). Data normality

was assessed through the Shapiro–Wilk test. As most variables were nonnormally distributed, the Wilcoxon signed–rank test was used for pre- and postoperative comparisons. Results were presented as median and range. P <0.05 was considered statistically significant.

Results

BCVA showed a median improvement from 0.46 logMAR (range, 0.10–0.78) at baseline to 0.38 logMAR (0.04–0.90) at 12 months; however, the change was not statistically significant (P = 0.15). Endothelial cell density showed no significant change (P = 0.144). CCT and TCT showed statistically significant reductions postoperatively (P < 0.001 for both). Kmax slightly decreased from 56.9 D (54.2–60.5) preoperatively to 55.6 D (53.0–58.7) postoperatively, but this difference was not statistically significant (P = 0.89). Km exhibited minimal variation, from 48.7 D (46.0 to 51.2) preoperatively to 48.3 D (46.1–50.8) postoperatively, with no statistical significance (P = 0.76). Keratoconus indices (KI and CKI) remained stable during the study period. A summary of keratometric and structural parameters is provided in Table 1.

mfERG analysis revealed no statistically significant changes in P1 wave amplitudes or implicit times across all analyzed macular rings. In Ring 1, the median P1 wave amplitude was 831 nV (range 109–1529) preoperatively and 898 nV (527–1135) postoperatively, with no significant difference (P = 0.454). P1 wave amplitudes and implicit times in Rings 2–5 remained stable, with no statistically significant changes compared to baseline values [Table 2 and Figures 1, 2].

EDI-OCT assessments showed no significant changes in LA, TCA, or choroidal vascularity index (CVI). Median LA was 360 μm² preoperatively and 361 μm² postoperatively (P = 0.71); similar nonsignificant changes were observed in TCA and CVI [Table 3]. No intraoperative or postoperative complications occurred. All bandage contact lenses were removed uneventfully in the first postoperative week, with no adverse events or patient-reported discomfort during follow-up.

Discussion

This study evaluated the safety and efficacy of an accelerated continuous cross-linking (CXL) protocol with a total energy dose of 7.2 J/cm² in patients with progressive keratoconus.

The findings indicate that this protocol effectively stabilizes keratoconus progression while preserving macular function and choroidal vascular integrity over 12 months. Notably, the absence of significant changes in macular structure and function strengthens the safety profile of this approach, especially in the context of concerns regarding potential posterior segment damage associated with high-intensity UV-A exposure.[1,2]

Although the improvement in BCVA was not statistically significant, the trend toward better visual outcomes suggests maintained or slightly improved retinal image quality following treatment. Similarly, keratometric parameters (Kmax, Km) and keratoconus indices (KI, CKI) remained stable, supporting the efficacy of this protocol in halting disease progression. These findings are consistent with prior studies demonstrating the biomechanical benefits of accelerated CXL protocols and the use of dextran-free riboflavin formulations.[3-6]

Importantly, the significant postoperative reductions observed in CCT and TCT are consistent with known stromal compaction effects following crosslinking. This finding reflects transient corneal remodeling rather than true tissue loss. Meanwhile, endothelial cell density remained stable postoperatively, confirming that the protocol does not compromise endothelial viability even in corneas approaching lower thickness limits. Together, these parameters reinforce the anterior segment safety profile of this accelerated CXL approach.[5-7]

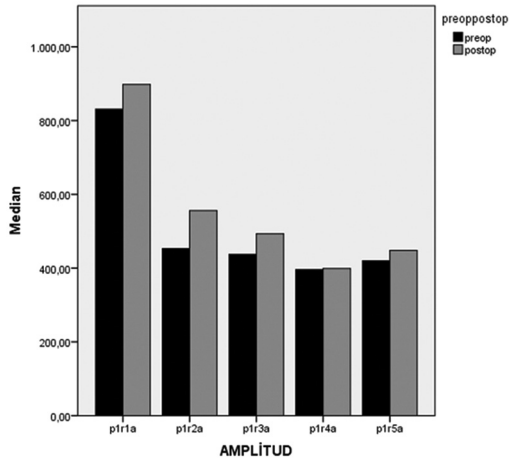

Figure 1: Preoperative and postoperative P1 wave amplitudes measured by multifocal electroretinography. P1 wave amplitudes recorded in five concentric rings (R1–R5) from the fovea to the outer macula show no significant changes after accelerated CXL treatment

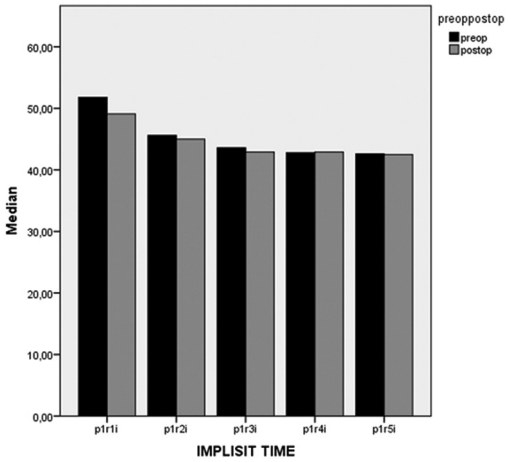

Figure 2: Preoperative and postoperative implicit times measured by multifocal electroretinography. Implicit times recorded in five concentric rings (R1–R5) from the fovea to the outer macula remain stable following accelerated CXL treatment

Table 1: Comparison of keratometric parameters and best-corrected visual acuity before and 12 months after accelerated corneal cross-linking

Parameter	Preoperative, median (minimum–maximum)	12-month postoperative, median (minimum–maximum)	*P*
BCVA (logMAR)	0.46 (0.10–0.78)	0.38 (0.04–0.90)	0.15[a]
Endotel cell count, mean±SD	2615±251	2571±207	0.144[b]
CCT (µm), mean±SD	475.69±34.09	453.97±38.07	<0.001[a]
TCT (µm), mean±SD	465.75±33.53	443.71±37.97	<0.001[a]
Kmax	57.3 (51.7–70.4)	57.0 (51.3–68.8)	0.89[a]
Km	48.3 (43.5–56.1)	49.2 (43.5–56.5)	0.76[a]
KI	1.21 (1.07–1.53)	1.25 (1.11–1.46)	0.18[a]
CKI	1.06 (1.02–1.21)	1.07 (1.03–1.52)	0.18[a]

Statistical tests: [a]Wilcoxon signed–rank test, [b]Paired samples *t*-test. BCVA: Best-corrected visual acuity, Kmax: Maximum keratometry, Km: Mean keratometry, KI: Keratometric ındex, CKI: Central keratometric ındex, CCT: Central corneal thickness, TCT: Thinnest corneal thickness, SD: Standard deviation

Table 2: Preoperative and 12-month postoperative multifocal electroretinography results

	P1 wave					
Rings	Amplitude (nV), median (minimum–maximum)			Implicit time (ms), median (minimum–maximum)		
	Preoperative	12-month postoperative	*P*	Preoperative	12-month postoperative	*P*
R1	831 (109–1529)	898 (527–1135)	0.454	51.8 (45.2–54.1)	49.1 (43.9–54.7)	0.433
R2	453 (296–651)	556 (306–781)	0.150	45.6 (43.0–47.6)	45.0 (41.1–48.8)	0.231
R3	437 (321–636)	493 (287–690)	0.973	43.6 (41.1–46.5)	42.9 (40.5–44.9)	0.322
R4	396 (249–737)	399 (264–590)	0.413	42.8 (41.3–45.4)	42.9 (40.6–44.9)	0.586
R5	420 (299–660)	448 (324–616)	0.518	42.6 (41.1–44.5)	42.5 (40.6–44.1)	0.375

Comparison of P1 wave amplitudes and ımplicit times across concentric retinal rings (R1–R5) in keratoconus patients treated with accelerated CXL. R1–R5: Stimulus rings from the central (R1) to peripheral (R5) retina, P1 wave amplitudes are expressed in nanovolts (nV), and implicit times in milliseconds (ms). Wilcoxon signed–rank test (used for paired, nonparametric comparison of pre- and post-treatment data). CXL: Corneal collagen crosslinking

Table 3: Comparison of enhanced depth imaging optical coherence tomography parameters before and 12 months after accelerated corneal cross-linking

Parameter	Preoperative, median (minimum–maximum)	12-month postoperative, median (minimm–maximum)	*P*
LA (µm²)	360 (269–602)	361 (268–547)	0.71
TCA (µm²)	572 (419–1036)	557.5 (398–907)	0.47
CVI	0.61 (0.58–0.70)	0.62 (0.60–0.69)	0.26
1500 µ SA (µm²)	113 (82–192)	113.5 (80–176)	0.75
1500 µ TA (µm²)	176 (119–327)	174.5 (112–285)	0.71
1500 µ CVI	0.60 (0.54–0.69)	0.62 (0.58–0.73)	0.47

All areas are in square micrometers (µm²). Statistical test: Wilcoxon signed–rank test. EDI-OCT: Enhanced depth imaging optical coherence tomography, LA: Luminal area, TCA: Total choroidal area, CVI: Choroidal vascularity index

With respect to posterior segment safety, the stability of choroidal vascular parameters, including LA, TCA, and choroidal vascularity index (CVI), suggests no deleterious effects on choroidal perfusion. These results suggest that the accelerated protocol minimizes UV-A-related damage to posterior segment structures, consistent with prior studies demonstrating the negligible impact of similar energy doses on the retina and choroid.[7-9]

Functional macular assessment through mfERG revealed no significant changes in P1 wave amplitudes or implicit times across concentric rings. This electrophysiological stability further indicates that the protocol does not induce subclinical retinal dysfunction, even in regions close to the UV-A exposure path. These results align with preclinical models and human data suggesting negligible retinal exposure with current CXL techniques.[10-13]

In addition, no intraoperative or postoperative complications were recorded. Epithelial healing occurred uneventfully, and no patients exhibited corneal haze, lenticular opacities, or subjective visual disturbances during follow-up. The shortened irradiation time and use of dextran-free riboflavin may contribute to enhanced patient comfort and faster recovery, especially in individuals with thinner corneas.[10-12]

While these findings support the short-term safety and efficacy of this accelerated continuous CXL protocol, further research involving larger cohorts and longer follow-up is essential to confirm long-term stability, refractive outcomes, and posterior segment integrity. Integration of newer imaging biomarkers and functional tests may also enhance future safety assessments.[13,14]

Conclusion

This study demonstrated that the accelerated continuous cross-linking (CXL) protocol delivering a total energy dose of 7.2 J/cm² is a safe and effective treatment for progressive

keratoconus. The protocol provides significant clinical benefits by preserving visual acuity, corneal biomechanical stability, and macular and choroidal integrity, without compromising corneal endothelial density or inducing significant corneal thinning beyond expected stromal remodeling. The absence of significant intraoperative or postoperative complications further underscores its safety, making it a viable alternative to conventional Dresden protocols.

The shorter treatment duration and dextran-free riboflavin offer practical advantages, particularly for patients with thinner corneas or those at risk of retinal complications.[15,16] While these findings are encouraging, larger and longer-term studies are warranted to further validate the sustained safety and efficacy of this accelerated CXL protocol.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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