

Complications of Corneal Collagen Cross-Linking: A Literature Review

Korneal Kollajen Çapraz Bağlama Tedavisinin Komplikasyonları: Literatür Taraması

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Abstract

Corneal crosslinking [CXL] is the first promising surgical procedure that halts the progression of corneal ectatic disorders. CXL is a technique that uses riboflavin and ultraviolet A [UVA] light to induce corneal stiffening by increasing the number of intra- and interfibrillar covalent bonds and corneal collagen resistance against enzymatic degradation. Recent studies suggest that CXL can also have beneficial effects with few complications. With more widespread application of CXL, reports of complications are increasing. Ophthalmologists should be encouraged to report all complications of CXL since early diagnosis and proper treatment can improve success rate of this new technique.

Key Words: Complications, Corneal Crosslinking, Corneal ectatic disorders

Özet

Korneal çapraz bağlama [CXL], korneal ektatik hastalıkların ilerlemesinin durdurulmasında ilk umut vaat eden cerrahi uygulamadır. Bu tedavi, riboflavin ve ultraviyole A ışığı kullanarak korneadaki intra- ve interfibriller kovalan bağların sayısını arttırmakta, korneanın güçlenmesini ve enzimatik yıkıma karşı dirençli hale gelmesini sağlamaktadır. Son zamanlarda yapılan çalışmalarda, CXL'in pek çok yararlı etkisinin yanında bazı komplikasyonları bildirilmiştir. CXL'in çok sık kullanılmaya başlanması ile birlikte komplikasyon bildirimleri de artmaktadır. Bu yeni tekniğin komplikasyonlarının iyi bilinmesi, erken tanı konulması ve tedavisi ile başarı oranı artacaktır.

Anahtar Kelimeler: Komplikasyonlar, Korneal ektatik hastalıklar, Korneal kroslinkig

Riboflavin (photosensitizer, vitamin B2) and ultraviolet A (UVA) light-induced collagen cross-linking of the cornea (CXL) is a novel technique that aims to improve the mechanical and biochemical stability of the stromal tissue [1]. This is the first surgical procedure to halt the progression of corneal ectatic disorders such as keratoconus [2], pellucid marginal degeneration [3, 4], and ectasia after excimer refractive surgery [5, 6]. Furthermore, this procedure is now being used

for nonectatic disorders such as corneal edema [7, 8] and infectious keratitis [9-11].

Although CXL is a promising technique for many corneal disorders, associated complications must be considered to determine the correct technique, select the correct patients, and increase the success. This study reviews the literature on CXL complications.

Technique

After instillation of a topical anesthetic, the central 7–9 mm of the cornea is debrided to allow homogenous diffusion of riboflavin into the stroma. Subsequently, riboflavin 0.1% drops are instilled every 3 min for 30 min. These drops are prepared immediately before treatment by mixing aqueous riboflavin 0.5% solution with dextran T-500 20% solution. UVA light is applied at a

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wavelength of 370 nm and an irradiance of 3mW/cm² at a distance of 5.4 mm from the cornea for 30 min [2]. Antibiotic eye drops are instilled after surgery and a bandage contact lens is inserted, which is removed after epithelial healing is complete.

Complications of CXL

In general, CXL is considered to be a safe surgical procedure without sight-threatening complications [12-14]. However, previous studies have reported the following complications after CXL:

- Corneal haze
- Endothelial damage
- Infectious keratitis
- Diffuse lamellar keratitis
- Peripheral sterile infiltrates

Corneal Haze

Corneal haze is a common side effect of CXL, which potentially limits final visual acuity. It is a result of the corneal healing process [15-17]. Loss of keratocytes and changes in collagen structure are possible causes of haze after CXL [15, 18]. CXL-related haze has different clinical properties compared with the haze related to other surgical treatments such as photorefractive keratectomy (PRK). Although PRK-related haze is limited to the subepithelial area, CXL-related haze affects up to 60% of the stromal depth [17, 19]. CXL-related haze is a dust-like change in the corneal stroma or the midstromal demarcation line, whereas PRK-related haze has a more reticulated subepithelial appearance [20].

Raiskup et al. retrospectively evaluated 163 eyes of 127 keratoconus patients 1 year after CXL and concluded that the K-value and corneal thickness can be considered predictive factors for possible development of corneal haze after CXL. They also indicated that advanced keratoconus should be considered an important risk factor for haze development after CXL because of low corneal thickness and high corneal curvature [16].

Gutiérrez et al. evaluated the changes in corneal transparency after CXL, which were objectively measured using the Pentacam Scheimpflug corneal densitometry. They reported that corneal densitometry showed a transient increase in corneal transparency that recovered to baseline values after 3 months [18].

Greenstein et al. determined the natural history of CXL-related haze, measured using Scheimpflug imagery and slit-lamp biomicroscopy; 1 year after treatment, they reported a decrease in the clinical grade of the haze detected with the slit-lamp from grade 0.78 to 0.06. They also objectively quantified

corneal haze and found that it was greatest at 1 month, plateaued at 3 months, and decreased significantly between 3 months and 12 months after treatment [19].

Koller et al. studied anterior stromal haze and graded it with a scale used for patients after PRK [21]. The mean grades 1, 6, and 12 months after treatment were 0.78, 0.18, and 0.06, respectively.

Understanding the natural course of corneal haze will allow clinicians to predict the postoperative results. Further studies are needed to clarify the pathophysiology of corneal haze.

Table 1 summarizes previous studies on corneal haze after CXL.

Endothelial Damage

Standard CXL is limited to eyes with a corneal thickness of at least 400µm because of its cytotoxic effects on the corneal endothelium, crystalline lens, and other intraocular tissues [12, 22]. An irradiance of 0.37 mW/cm² is reportedly cytotoxic to the endothelial cell layer. Because the absorption coefficient of the human cornea is 70 cm⁻¹ and the intended surface irradiance is 3.0 mW/cm², a 0.37-mW/cm² irradiance is achieved at a depth of 300µm. In a 400µm thick cornea saturated with riboflavin, the irradiance at the endothelial level is 0.18 mW/cm², which is only 50% of the damage threshold. Therefore, the 400µm limit is considered to protect the endothelium and intraocular structures from the adverse effects of UV irradiation [22-24].

Sharma et al. assessed 350 patients with a corneal thickness of more than 400µm who underwent CXL and identified corneal edema in 10 (2.9%) patients. The patients were followed up for a mean period of 14 ± 4 months. Corneal edema decreased in four patients and was resolved in one patient. Penetrating keratoplasty was offered to five patients when the decrease plateaued at 3 months [25].

Kymionis et al. assessed corneal endothelium 1 year after CXL using corneal in vivo confocal microscopy and found no significant changes. The cell density and hexagonality did not change during the follow-up period [26]. Another study by Kymionis et al. showed significant endothelial cell count loss after standard CXL in corneas with central pachymetry of less than 400µm [27]. Gokhale reported a case of a patient with a corneal thickness of more than 400µm who was treated using CXL. One month after CXL, the patient presented with massive corneal edema, which did not resolve despite intense therapy. Thus, the corneal thickness is not the only factor related to corneal endothelial damage after CXL [28].

Table 1. Studies related with corneal haze after CXL in the literature

Author*	Patients	Follow-up	Results	Conclusions
Raiskup ¹⁶	163 eyes of 127 patients with stage I-III keratoconus	1 year	9% clinically significant haze	Advanced keratoconus should be considered at higher risk of haze development after CXL due to low corneal thickness and high corneal curvature.
Gutiérrez ¹⁸	22 eyes of 15 patients with keratoconus	1 year	Immediately after CXL, corneal densitometry increased significantly. At 6 month follow-up, densitometry values were reduced.	Corneal densitometry showed a transient increase that recovered to baseline values after 3 months.
Greenstein ¹⁹	50 eyes of 44 patients (31 keratoconus and 19 post-LASIK ectasia)	1 year	The mean preoperative corneal densitometry was 14.9 ± 1.93 (SD). Densitometry peaked at 1 month (mean 23.4 ± 4.40 ; $P < .001$)	Corneal haze was greatest at 1 month, plateaued at 3 months, and was significantly decreased between 3 months and 12 months
Koller ²¹	117 eyes of 99 patients with keratoconus	105 completed the 1 year follow-up	Anterior stromal haze with a mean of 0.78, 0.18, and 0.06 at 1, 6, and 12 months, respectively	Preoperative maximum Keratometry reading was a significant risk factor for failure. Restricting patient age to younger than 35 years may reduce the complication rate to 1%.

*First author and reference

Table 2. Summarizes the literature reports on endothelial damage after CXL

Author	Patients	Results	Conclusions
Sharma ²⁵	350 patients with keratoconus	Corneal edema was determined in 10 (2.9%) patients.	2 patients underwent PK
Kymionis ²⁶	5 eyes with post-LASIK keratectasia and 5 eyes with keratoconus	The cell density and hexagonality of corneal endothelium was not found altered.	The corneal endothelium did not undergo any significant changes during follow-up period.
Kymionis ²⁷	14 eyes of 12 patients	Preoperative endothelial cell density was 2733 ± 180 cells/mm ² , at last visit 2441 ± 400 cells/mm ² ($p < .01$)	CXL in thin corneas seems to result in a significant endothelial cell density decrease postoperatively.
Gokhale ²⁸	Case report	Presented with massive corneal edema 1 month after CXL	Despite intense treatment, corneal scar remained.
Bagga ²⁹	Case report	Keratouveitis and generalized corneal edema seen 3 weeks after CXL. At 6 month visit, corneal edema increased with formation of epithelial bullae.	PK was performed.

*First author and reference

Bagga et al. reported a case of a patient who developed endothelial decompensation after CXL, for which penetrating keratoplasty was required [29].

Infectious Keratitis

The clinical presentations of keratitis after CXL differ depending on the etiologic agent. Keratitis after CXL has been related to bacteria

(*Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus* spp., and *Streptococcus* spp.) [30-33], herpes simplex virus [34, 35], and *Acanthamoeba* [36].

The possible mechanisms of infectious keratitis are keratocyte apoptosis secondary to UVA irradiation, impaired integrity of the epithelium, preoperative instillation of topical anesthetic agents, postoperative use of topical corticosteroids, nonsteroidal antiinflammatory drugs, and application of bandage soft contact lens to debrided corneas.

Cases of infections after CXL probably occur during the early postoperative period. It is known that CXL with UVA damages keratocytes but also kills bacteria and fungi. This is an advantage of using CXL to treat infectious keratitis [9].

Two cases of herpetic keratitis after CXL, which did not have a history of previous herpetic eye disease or cold sores, have been reported [34, 35]. HSV reactivation in the cornea can be triggered by various stimuli including trauma, fever, emotional stress, corneal surgery, and UV light. CXL involves epithelial and stromal trauma, damage to the subepithelial nerve plexus, UVA irradiation, and the use of topical corticosteroids, all of which are potential triggers.

A case of a patient with *Acanthamoeba* keratitis was reported where in the patient was unaware that he was wearing a bandage contact lens and repeatedly washed his face and eyelids with tap water. Corneal perforation was detected at follow-up, and therapeutic penetrating keratoplasty was performed. The patient's best corrected visual acuity was 20/40 with pinhole [36].

Bacterial keratitis with *P. aeruginosa*, *E. coli*, and *Staphylococcus epidermidis* have been reported after CXL [30-32]. Polymicrobial keratitis caused

by *Streptococcus salivarius*, *Streptococcus oralis*, and a coagulase-negative *Staphylococcus* spp., which was related to poor contact lens hygiene, has also been reported [33].

Koppen et al. reported four cases of severe keratitis in 117 keratoconic eyes treated with CXL [37].

Diffuse Lamellar Keratitis

Diffuse lamellar keratitis (DLK) is another complication that may occur after CXL. A patient with post-LASIK ectasia who developed DLK after CXL was treated with intensive topical corticosteroids and DLK resolved during the following 2 weeks [38].

Peripheral Sterile Infiltrates

Sterile infiltration after CXL may be related to cell-mediated immunity to the staphylococcal antigens that accumulate in areas of static tear pooling beneath the bandage contact lens [39]. In a study reported by Koller et al., sterile infiltrates occurred in 7.6% of eyes [21].

Conclusions

CXL is safe and effective with few known side effects. In future, CXL will probably be the most popular treatment option for corneal ectatic disorders because it minimizes the percentage of patients who need PRK.

However, reports of complications are increasing with more widespread application of CXL. Thus, more studies are necessary for identifying and successfully managing rare complications. Ophthalmologists should be encouraged to report all CXL-related complications because early diagnosis and proper treatment can improve the success rate of this new technique.

Table 3. Summarizes previous studies related to infectious complications of CXL

Author*	Organism	Follow-up (months)	Postoperative BCVA	Results
Sharma ³⁰	<i>Pseudomonas aeruginosa</i>	2	20/200	Leucomatous corneal opacity
Pollhammer ³¹	<i>Escherichia coli</i>	4.5	20/63	Avascularized stromal scar
Pérez-Santonja ³²	<i>Staphylococcus epidermidis</i>	5	20/22	Mild residual haze in the upper midperipheral cornea
Zamora ³³	<i>Streptococcus salivarius</i> , <i>Streptococcus oralis</i> , and coagulase-negative <i>Staphylococcus</i> sp.	2	20/50	Central corneal stromal haze and ring-like subepithelial scar
Kymionis ³⁴	Herpes Simplex	2	20/25	Mild paracentral subepithelial opacity
Yüksel ³⁵	Herpes Simplex	1	20/25	Mild paracentral subepithelial opacity
Rama ³⁶	<i>Acanthamoeba</i>	2 (after PK)	20/40	Clear graft

BCVA: Best Corrected Visual Acuity, *First author and reference

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