Efficacy and Safety of Standard Corneal Cross-Linking Procedures Performed With Short Versus Standard Riboflavin Induction: A Save Sight Keratoconus Registry Study

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Purpose: The objective of this study was to compare the effectiveness and safety of short versus standard riboflavin induction times in cross-linking (CXL) for keratoconus.

Methods: A retrospective comparative study was conducted with data from the Save Sight Keratoconus Registry. Inclusion criteria were epithelium-off technique, standard UVA CXL protocol (3 mW/cm^2 for 30 minutes), riboflavin induction for 15 minutes (short) or 30 minutes (standard), and 1 year of follow-up data after CXL. Outcome measures included changes in best-corrected visual acuity (BCVA), keratometry in the steepest meridian (K2), maximum keratometry (Kmax), thinnest pachymetry (TCT), and adverse events. Analysis was conducted using mixed-effects regression models adjusted for age, sex, visual acuity, keratometry, pachymetry, practice, and eye laterality.

Results: Two hundred eighty eyes (237 patients; mean, 27.3 ± 10.5 years old; 30% female) were included. The riboflavin induction time was short in 102 eyes (82 patients) and standard in 178 eyes (155 patients). The baseline characteristics (sex, mean age, BCVA, keratometry, and pachymetry [TCT]) were similar between the groups. At the 1-year follow-up visit, no statistically significant differences were observed in flattening in K2 and improvement in BCVA. Greater Kmax flattening [−1.5 diopters (D) vs. −0.5D, $P = 0.031$] and a greater proportion of >2% increase in TCT (23.5 vs. 11.3, $P = 0.034$) and haze (29 vs. 15, $P = 0.005$) were observed with short riboflavin induction.

Conclusions: Short and standard riboflavin induction times achieved similar degrees of flattening in K2 and improvement in vision. Greater improvements in Kmax and TCT were seen with short riboflavin times; however, this group had higher rates of haze.

Key Words: keratoconus, riboflavin, registries, disease progression, corneal cross-linking

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Keratoconus (KCN) is an ectatic disease of the cornea in which thinning and protrusion reduce visual acuity due to irregular astigmatism, high-order aberrations, and scarring.[1–3] It is a chronic condition that progressively reduces quality of life.[4–6] There are 2 important aspects in its management: the prevention of progression and improvement of visual acuity. Glasses, contact lenses or scleral lenses, intrastromal ring segments (ICRS), and/or corneal transplantation can improve vision depending on disease severity and corneal transparency.[1]

Risk factors for progression include: age younger than 30-year-old, eye rubbing, sleeping posture, and more severe KCN.[1,7,8] Criteria to determine progression include changes in visual acuity (VA), refraction, and the shape and aberrations of the cornea.[1,9,10]

Wollensack et al in 2003[11] published a new technique named cross-linking (CXL). In CXL, new covalent bonds between the collagen fibers of the corneal stroma are formed using free radicals after applying UVA light and riboflavin drops to a nonepithelized cornea. This technique has been proven to strengthen the cornea to prevent disease progression in long-term.[12] The first report of CXL surgery, known as the Dresden protocol, consisted of removal of the corneal epithelium, instilling riboflavin drops every 5 minutes for 30 minutes (induction), followed by UVA light exposure for 30 minutes at 3 mW/cm^2.[11] The Dresden protocol had the limitation of being a long procedure, this affected patient comfort and corneal dehydration, increasing the risk of thinning and infection during the procedure.[13–16] To reduce treatment times, variations in CXL protocols have arisen.[13–17] Different riboflavin induction times have been used across the globe. To the best of our knowledge, there are no published studies on the comparative effectiveness of different riboflavin induction times during CXL.

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TABLE 4. Secondary Outcomes of the Corneal Cross-Linking Protocols With Short (15 Minutes) and Standard (30 Minutes) Riboflavin Induction

	Riboflavin for 15 min	Riboflavin for 30 min	*P*
Minimum corneal thickness (MCT), μm			
Baseline, mean (SD)	476.6 (34.9)	449.1 (39.4)	<0.001
Change in crude mean (95% CI)	−9.6 (−16.4 to −2.8)	−15 (−19.4 to −10.7)	0.19
Change in adjusted mean (95% CI)	−12.4 (−26.4–1.6)	−14.6 (−23.8 to −5.5)	0.77
Increase >2%, %	23.5	11.3	0.034
Decrease >2%, %	42.6	54.0	0.16
Adverse events within 365 days post-CXL, n events (n eyes, % eyes)*			
Clinically significant haze	29 (18, 17.6%)	15 (11, 6.2%)	0.005
Scarring	3 (2, 2.0%)	4 (4, 2.2%)	1.0
Sterile infiltrates	1 (1, 1.0%)	1 (1, 0.6%)	
Stromal edema	2 (2, 2.0%)	1 (1, 0.6%)	
Microbial keratitis	4 (1, 1.0%)	—	
Recurrent corneal erosion	—	1 (1, 0.6%)	

**P* values are calculated for the difference in 'number of eyes' with the occurrence of an adverse event between the CXL protocols.
CXL, cross-linking.

Some studies indicate that riboflavin is not only a generator of free radicals but also a radical scavenger at high concentrations, which means that an increase in its concentration does not mean more effectiveness of CXL. It is hypothesized that a higher amount of riboflavin in the stroma can be detrimental for the efficiency of the CXL due to the more rapid consumption of oxygen by the riboflavin, which is needed for the creation of the new links between the collagen fibers.[14,23] This may explain the results obtained in our study. Riboflavin carriers also have an influence on the process.[32] Riboflavin with HPMC (hydroxypropyl methylcellulose) seems to penetrate deeper in the stroma and to generate a stronger reaction with more keratocyte loss compared with that with dextran.[32]

In terms of safety, we found higher rates of haze in the short group and this could be also a consequence of the above. Haze after CXL is the most common complication, and it is produced because of keratocyte death and fibroblasts that disturb corneal structure and reduce corneal transparency.[32] Haze appears deep in the stroma, and it is usually temporary, improving in the first months with the help of topical steroids.[17,30] Cases of persistent haze are due to the presence of superficial myofibroblasts caused by delays in epithelial healing or abnormal re-epithelization of any reason.[32] Pecorella et al[33] reported worst postoperative haze with less riboflavin soaking time and with more UVA time. A recent study by Marcovich et al [34] compared in vitro corneal responses with different induction riboflavin times (10 minutes vs. 30 minutes) and found that shorter riboflavin times may prevent potential endothelial toxicity. In our study, haze rates were higher in the short group (17.2% vs. 6.2%, $P = 0.005$), consistent with what is reported in the literature.[33] The mostly temporary nature of corneal haze and lack of effects on vision in long-term was confirmed in our study, in which visual outcomes at follow-up were comparable between the 2 groups.

Our study had some limitations. First of all, different specialists, measurement methods, and techniques were used because of the nature of the SSKR which collects real-world outcomes. Although this should be taken into account when interpreting the results, it also provides insights into real clinical conditions, in which homogeneity is not possible, and may have some advantages. Furthermore, multivariable analysis controlling potential confounders was used to minimize this limitation. Endothelial toxicity and impact of drops regimens were not assessed in this study. Further the short follow-up period of 1 year means that stability of the results must be confirmed by studies with longer follow-up periods. Therefore, studies with longer follow-up and more homogeneous data are required to confirm our findings. The SSKR's recently launched Optometry Module has the capacity to collect long-term data for patients with keratoconus who are primarily seen by their optometrist after CXL.[19]

In conclusion, a shorter riboflavin induction time was effective and safe in real-world settings for CXL with benefits for corneal shape, thickness, and operative time. Clinicians should be aware that increased rates of corneal haze may occur with shorter riboflavin times.

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