The Dynamic Safety for Cross-Linking in Thin Corneas With Extra Protection Under a Contact Lens

In the article “Contact Lens-Assisted Collagen Cross-Linking (CACXL): A New Technique for Cross-Linking Thin Corneas” by Jacob et al., the authors proposed a contact lens for extra protection of corneal collagen cross-linking (CXL) in thin corneas (range: 350 to 498 µm; mean: 377 µm). In their study, the treated corneas are protected by the contact lens and riboflavin (B2). I intend to provide a detailed analysis regarding the safety issues in the above described two-layer system. Furthermore, I will demonstrate that contact lenses are not the only safety solution for thin corneas, where low doses may be applied for thinner corneas.

The safety dose (with a contact lens) may be expressed as

\[ E(z) = E^* \cdot \exp(aD) \]  \hspace{1cm} (1)

where \( E^* \) is the safety dose \(^2\) without the contact lens; \( a \) (in cm\(^{-1} \)) is the ultraviolet (UV) light absorption coefficient of the contact lens (having a thickness \( D \) in cm). For a contact lens (100-µm thick) and an absorption coefficient at UV 365 nm, \( a = 32 \) cm\(^{-1} \), I find \( E = 1.38E^* \) (in J/cm\(^2\)). That is, the extra contact lens protection allows a 38% more safety dose suitable for thin corneas (range: 350 to 400 µm). However, thin corneas can be treated safely by a lower dose \( (E^*) \), rather than contact lens protection, to be discussed as follows.

The safety dose without the contact lens \( (E^*) \) in equation 1 is given by a revised \( E^* \) formula\(^3\) in the linear approximation (corneal thickness range: 350 to 450 µm), for B2 concentration of 0.1% and 0.2%, respectively,

\[ E^* = 3.12 + 0.0123(z-400) \] \hspace{1cm} (2a)

\[ E^* = 7.8 + 0.036(z-400) \] \hspace{1cm} (2b)

where \( E' \) is the cytotoxic energy threshold of endothelial cells, reported to be 0.32 J/cm\(^2\). For a typical penetration depth of 300 µm and corneal thickness \( z = (350, 400, 500) \) µm, I find the safety dose \( E^* = (2.5, 3.12, 3.73) \) J/cm\(^2\), for \( C = 0.1\% \), which increases to \( E^* = (6.0, 7.8, 9.6) \) J/cm\(^2\) for a higher \( C = 0.2\% \).

If no B2 surface layer is present during the UV exposure, for a thin cornea thickness of 380 µm with a penetration depth of 300 µm and contact lens protection (100-µm thick), I find the allowed safety dose is \( E = 1.38E^* = 1.38 \times 2.87 = 4.0 \) J/cm\(^2\), for B2 concentration \( C = 0.1\% \). Therefore, without the extra protection of the B2 surface layer, the conventional dose of 5.4 J/cm\(^2\) is not safely protected by the contact lens.

With the existence of the B2 surface layer,\(^4\) the effective dose is reduced by a factor \( R \), with \( R = (0.69, 0.48) \), for B2 concentration \( C = (0.1\%, 0.2\%) \), and a typical thickness of 100 µm. Therefore, the safety dose increases to \( E^*/R = (1.4 \text{ to } 2.0) E^* \), with the extra protection of the B2 surface layer. I note that the surface depletion dose, given by \( (1-R)E^* \), is the wasted dose in depleting the surface B2 layer before the UV light could effectively transmit into the stroma. For efficient CXL, no B2 should be applied during the UV exposure and any extra B2 should be washed off completely. Greater detail for the discussion of CXL efficacy can be found elsewhere.\(^4\)

My formulas given by equation 2 show that without the use of contact lens and no extra B2 surface layer, thin corneas must be treated under a low dose \( E^* = (range: 2.5 \text{ to } 3.8) \) J/cm\(^2\), for a corneal thickness range of 350 to 400 µm, and under a typical concentration of \( C = 0.1\% \). A higher safety dose of \( E^* = (range: 6.0 \text{ to } 9.6) \) J/cm\(^2\) is allowed for a higher concentration, \( C = 0.2\% \), and penetration depth of 300 µm.

I emphasize that, within the safety dose criteria, lower dose is always preferred for accelerated CXL procedures. However, the efficacy (or the B2 depletion level) is proportional to the total dose applied on the cornea. Therefore, optimization between these two competing factors is required for a fast and efficient CXL. A high safety dose may be achieved by either higher B2 concentration or a larger penetration depth. The commonly accepted criteria of corneal thickness larger than 400 µm under a fixed dose of 5.4 J/cm\(^2\) is just one of my safety conditions. From my new formulas, the conventional set of parameters (> 400 µm, 5.4 J/cm\(^2\)), in many situations, are not safe when a low B2 concentration is used (\( C < 0.15\% \)) and penetration depth is less than 200 µm. For efficient and fast CXL, no B2 should be applied on the cornea surface during UV light exposure.

REFERENCES


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Dr. Lin is the CEO and founder of, receives fees from, and hold a patent with New Vision, Inc.
Reply:

We thank Dr. Lin for his interest in our article on contact lens-assisted corneal cross-linking (CACXL). We agree that CXL can be attained in thin corneas without contact lens by titrating the ultraviolet (UV) irradiance. In CACXL, the role of the riboflavin-soaked contact lens is to decrease the amount of actual excess irradiation to the corneal stroma while providing an additional working layer along with the photosensitizer. The contact lens we used did not have inherent UV absorbing monomer in it. From the original research of Dr. Lin, we observed the depleting nature of riboflavin (B2) on UV irradiation as explained by the analytical formulas in dynamic cornea model. In existing CXL devices, the UV light irradiance is administered for 30 minutes after instillation of B2 for 30 minutes in the corneal stroma. According to the conventional protocol (the Dresden protocol), the minimum corneal thickness is the vital factor to prevent endothelial damage. However, B2 depletion and time-dependent change in cross-linking has been reported.

It has been shown that the progressive mode of UV irradiance is safer than the conventional continuous mode of UV light irradiance. The principle reason behind this is that during the initial minutes of UV exposure, there is less cross-linking happening because of an excess B2 layer and as time passes cross-linking increases due to initiator depletion. However, there are no clinical trials showing the same effect in human corneas. Two critical parameters, namely the safety depth (z*) and the cross-linking time (T*), were analyzed via numerical and analytic formulas. A higher light intensity and a smaller initiator concentration require a shorter cross-linking time to achieve a given cross-linking depth. However, we believe this can be correlated more when the original parameters are changed in accelerated CXL where the intensity and time can be modified and the time of exposure is often shorter. In CACXL, the UV irradiance is kept equal throughout the procedure (no change in intensity from the device or change in time irradiated), and the B2 layer is treated similar to the conventional method in normal corneas as described by Wollensak.

In our clinical trial, which was done as a pilot study, we noted no regression of cornea after 1 year and the demarcation line attained was as deep as 270 µm. We were able to treat corneas ranging from 350 to 390 µm. According to Dr. Lin’s analytical formula, thin corneas with a corneal thickness range of 350 to 400 µm can be treated under a low dose without the use of contact lens and no extra B2 surface layer. In CACXL, UV-A transmission through the soaked contact lens at the level of the cornea was 1.5 to 1.7 mW/cm². This was approximately 50% to 60% of the irradiance of conventional CXL in normal corneas. We were able to obtain cross-linking up to the mean depth of 252.9 ± 40.8 µm in corneas with a mean minimum corneal thickness after epithelial removal of approximately 377.2 ± 14.5 µm.

The main objective of CACXL is to make cross-linking possible in thin corneas without any additional protocol variation while obtaining effective cross-linking at the desired level. Although the B2 layer on the contact lens is crucial to maintain the overall height, we noted the mean increase in layer thickness with and without the B2 layer on the contact lens was minimal. The increase in minimum corneal thickness after placing the contact lens with the B2 layer ranged from 90 to 124 µm. With newer devices that have an accelerated mode, Dr. Lin’s viewpoint of fast and effective cross-linking without the B2 layer during UV exposure has to be considered. We agree with Dr. Lin’s viewpoint that within the safety dose criteria, lower dose may be preferred for accelerated CXL procedures. A randomized clinical trial comparing low dose UV with CACXL can project more light on this hypothesis. Nevertheless, CACXL has shown no regression or recurrence in eyes with progressive keratoconus in the current treatment protocol. There were no endothelial cytotoxic features such as polymegathism or pleomorphism in the postoperative period and patients maintained endothelial count without significant loss (P = .63).

REFERENCES

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