Influencing Factors Relating the Demarcation Line Depth and Efficacy of Corneal Crosslinking

The recent article of Spadea et al.1,2 and Toker et al.3 evaluated the efficacy of accelerated corneal crosslinking (AXL) under different treatment protocols, and the relationship between CXL efficacy and the demarcation line (DL) depth based on available measured data.1,2 The sudden-drop of DL depth at high intensity (>45 mW/cm²) has the similar feature as the AXL efficacy reported by Wernli et al.4 However, it is clinically unclear whether DL depth is proportional to the crosslink depth or the CXL efficacy.1–3 Moreover, controversial results of AXL efficacy were reported due to inconsistent protocols which were not optimized. To improve the efficacy of AXL, Lin proposed a new protocol called riboflavin (Rf) concentration-controlled method (CCM),5 in which extra Rf drops are applied to the cornea at every crosslink time (7'), during the UV exposure, having a frequency defined as Fdrop = N – 1, with N = 0.365 [Io/C0]0.5. This formula provides the optimal protocol that higher intensity (Io) and/or lower Rf concentration (C0) requires larger Fdrop to compensate its faster Rf depletion, and lower steady-state efficacy, comparing to the low-intensity Dresden protocol.

This correspondence intends to further analyze the clinically measured DL depth via the key influencing factors of CXL, including Rf concentration profile (pre- and intraoperatively),6 Rf initial diffusion depth, UV light effective dose, epithelial absorption (for epi-on case), and most importantly, the administration protocols of Rf during CXL, governed by Fdrop and the waiting period after each Rf drop.5 The measured DL-depth of various protocols will be analyzed and compared to a combined-efficacy formula.5,6

The measured DL-depth may be compared to a combined type-I CXL efficacy given by $c$-Ceff = 1 - $e^{-R/D}$, with $R = (62/1') [C_e/FcC_t]/I_0^{0.5}$, where $F(z) = 1 - 0.5z/D$, is the Rf initial concentration profile defined by a diffusion depth ($D$); and the resupply Rf drops every $t'$ minutes. $R$ is the efficacy ratio between the noncontrolled Dresden protocol and the optimal protocol (via CCM) having $R = 1.0$, and $c$-Ceff = 0.98, for all range of UV intensity $I_0 = 3$ to 60 mW/cm².

Figures 1 and 2 show that the DL depth (based on measured data1,2) follows the similar decreasing trend as the calculated CXL efficacy in AXL. Figure 2 shows the theoretical curves (1, 2, 3, 4) calculated from the combined efficacy (c-Ceff) formula,5,6 with time of resupply Rf drops $t' = (4, 2, 1, 0.5)$ minutes. The measured DL-depth ($z^*$) and theorized efficacy are compared to conclude the following features:

1. In Figure 1, curve B for extended dose (6.2 J/cm²) has a larger $z^*$ than curve A (dose of 5.4 J/cm²). It is also predicted by Lin’s formula for crosslink depth5 which is proportional to light dose, rather than light intensity. Modern protocol has also suggested to use a higher dose of 7.2 J/cm², replacing the Dresden 5.4 J/cm² (operation manual of KXL, Avedro Inc.).

2. Epi-on is less efficient than epi-off due to limited diffusion depth ($D$) and the extra absorption of the epithelium; and epi-on CXL with iontophoresis has a larger $z^*$ due to improved diffusion depth ($D$), comparing data 1 and data 2 of Figure 1. This feature is also shown in Lin’s efficacy-formula,7 where higher $D$ has higher value of $F(z) = F(z) = 1 - 0.5z/D$ and leads to higher efficacy.

3. Curve 2 of Figure 2 represents the conventional protocol having resupply the Rf drops every 4 minutes. Therefore, it has the similar profile as curve A of Figure 1. This feature indicates that CXL efficacy is proportionally related to the DL depth. The recent article of Spadea et al.2 also concluded that the depth of DL is an indirect measurement of CXL penetration within the stroma, although “the deeper, the better” requires further clinical long-term studies.

4. Both CXL efficacy and DL depth have a cutoff maximum intensity, under the noncontrolled Dresden protocol, as reported by Wernli et al.4 It should be noted that the theoretical curve 4 (with controlled $t' = 0.5$ minute, or Fdrop = 5 to 4) gives the optimal efficacy comparable to CCM.5

5. In contrast to the conventional belief (by Hafezi and Kling et al.) that oxygen-mediated type-II plays the critical role of CXL, Kamaev et al.8 kinetic model showed that CXL is predominated by type-I, while
oxygen (or type-II) only plays a limited and transient role. Lin’s 3-pathway model\(^9\) showed mathematical details of the role of oxygen, supporting the claim of Kamaev et al.\(^8\) In addition, a recent clinical study of Lombardo et al.\(^10\) showed a simple-exponential kinetic of RF concentration also implied that, in ambient environment (with approximately 21% partial pressure of oxygen), nonoxygen-mediated type-I mechanism is predominant.

6. The conventional Dresden protocol, extra RF drops (with a frequency \(F_{\text{drop}} = 10-15\)) instilled during the UV exposure. This too-often \(F_{\text{drop}}\) will reduce the effective dose and CXL efficacy. Some modern protocols propose not to apply any extra RF drops (with \(F_{\text{drop}} = 0\)), however, has less efficacy than that of optimal CCM\(^5\) which requires \(F_{\text{drop}} = 3\) to 5 for high intensity AXL (18-50 mW/cm\(^2\)).

7. Extension of exposure time (or dose) in AXL may increase the crosslink depth (\(z\)) and improve the efficacy governed a crosslinked stroma volume \(z = \text{depth} \times \text{strength}\). Higher RF concentration (\(C_0\)) achieves higher efficacy, predicted by \(c\)-Ceff formula\(^7\) was also clinically reported by O’Brart et al.\(^11\) Therefore, new clinical studies of DL-depth for a wider range of \(C_0 = 0.1\%\) to 0.3%, and under the CCM protocol might lead to a breakthrough of the AXL efficacy and justify the accuracy of CCM for optimal efficacy.

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References

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