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

The recent article of Spada et al.\textsuperscript{1,2} and Toker et al.\textsuperscript{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.\textsuperscript{1-5} The sudden-drop of DL depth at high intensity (>45 mW/cm\textsuperscript{2}) has the similar feature as the AXL efficacy reported by Wernli et al.\textsuperscript{4} However, it is clinically unclear whether DL depth is proportional to the crosslink depth or the CXL efficacy.\textsuperscript{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),\textsuperscript{5} in which extra Rf drops are applied to the cornea, at every crosslink time ($T$), during the UV exposure, having a frequency defined as $F_{\text{drop}} = N - 1$, with $N = 0.365 \left[ I_0 / C_0 \right]^{0.95}$. This formula provides the optimal protocol that higher intensity ($I_0$) and/or lower Rf concentration ($C_0$) requires larger $F_{\text{drop}}$ 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),\textsuperscript{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 $F_{\text{drop}}$ and the waiting period after each Rf drop.\textsuperscript{5} The measured DL-depth of various protocols will be analyzed and compared to a combined-eficacy formula.\textsuperscript{5,7}

The measured DL depth may be compared to a combined type-I CXL efficacy given by $F_{\text{eff}} = 1 - \exp (-4R)$, which is $R = (62 / t') \left[ C_0 F(z) / I_0 \right]^{0.5}$, 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 $c$-$C_{\text{eff}} = 0.98$, for all range of UV intensity $I_0 = 3$ to 60 mW/cm\textsuperscript{2}.

Figures 1 and 2 show that the DL depth (based on measured data\textsuperscript{1,2}) 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 ($c$-$C_{\text{eff}}$) formula,\textsuperscript{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/cm\textsuperscript{2}) has a larger $z^*$ than curve A (dose of 5.4 J/cm\textsuperscript{2}). It is also predicted by Lin's formula for crosslink depth\textsuperscript{5} which is proportional to light dose, rather than light intensity. Modern protocol has also suggested to use a higher dose of 7.2 J/cm\textsuperscript{2}, replacing the Dresden 5.4 J/cm\textsuperscript{2} (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,\textsuperscript{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 Spada et al.\textsuperscript{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.\textsuperscript{4} It should be noted that the theoretical curve 4 (with controlled $t' = 0.5$ minute, or $F_{\text{drop}} = 3$ to 4) gives the optimal efficacy comparable to CCM.\textsuperscript{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.\textsuperscript{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 \(V = \text{depth} \times \text{strength}\). 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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