A Proposed Concentration-Controlled New Protocol for Optimal Corneal Crosslinking Efficacy in the Anterior Stroma

The recent article of Bekesi et al. made two important conclusions about corneal collagen crosslinking (CXL): Firstly, biomechanical properties determined after ex vivo CXL may not provide entirely accurate information about the responses to CXL in vivo; secondly, within the crosslinked regions, rose bengal crosslinking (RGX) stiffened the cornea to a greater degree than ultraviolet-A (UVA) crosslinking (UVX) at 1 and 2 months, suggesting a greater density of crosslinks produced by RGX. The intent of this letter is to provide mathematical formulas to analyze and comment on the above clinically measured features and also propose a new protocol called the riboflavin concentration-controlled method (CCM), which, as theoretically demonstrated, is more efficient than the conventional Dresden protocol (using a saturated concentration) or other noncontrolled concentration methods based on the Bunsen–Roscoe reciprocal law.

For type I, epi-off CXL, the efficacy is given by $S = \sqrt{(kF\text{C0}^2/\alpha X^2)} \quad [1 - \exp(-bX)]$, where $k$ is an effective rate constant; $X = \exp(-Az)$; $z$ is the stromal thickness; $A$ is an effective absorption coefficient given by $A = 2.5\text{maa}_0C_{\text{0}}(1 - 0.25z/D) + Q$; $b = 0.5a(\text{Io})_0$, $a = 0.622p$, $p$ being the quantum yield and $m = 1.5$ a fit parameter; $a$ and $Q$ are the absorption coefficient of the photolysis and the stroma, respectively. $C_0$ is the initial (at $t = 0$) riboflavin (RF) concentration having a bleaching effect in the anterior stroma (100–250 $\mu$m). Numerical simulation of $c$-Ceff (to be shown elsewhere) under the new CCM protocol shows a stronger bleaching effect in the anterior stroma (100-250 $\mu$m), which is re-treated by Fdrop times, and the waiting period (with UV off) after each RF drops secures enough diffusing depth ($D > 150 \mu$m). The above CCM proposes that higher intensity requires larger Fdrop (or more RF resupply) to compensate the faster depletion in the anterior stroma, especially in high intensity (>18 mW/cm²). In contrast to the conventional Dresden protocol, which keeps the RF in a saturated condition during the UV exposure, CCM proposes to turn off the UV light after each of the extra RF drops applied to the stroma and waiting for a period approximately 1.0 to 2.0 minutes to allow enough RF diffusion (with a diffusion depth $D > 150 \mu$m) before it is turned on again. In the above proposed CCM, my theory predicts comparable efficacy (for the same dose) for intensity of 1.5 to 45 mW/cm², based on a combined efficacy formula defined as $c$-Ceff = $1 - \exp [-\left(S_1 + S_2 + \ldots + s_l\right)]$, with $j = \text{Fdrop}$, and Fdrop is given by the integer portion of square root of $[\text{Io}/3]$, that is, Fdrop = (1, 1, 2, 3, 4), for $\text{Io} = (1.5, 3, 9, 18, 30, 45) \text{ mW/cm²}$ and exposure time $t = (30, 30, 10, 5, 3, 2) \text{ minutes}$. The above CCM proposes that higher intensity requires larger Fdrop (or more RF resupply) to compensate the faster bleaching effect in the anterior stroma (100-250 $\mu$m), which is re-treated by Fdrop times, and the waiting period (with UV off) after each RF drops secures enough diffusing depth ($D > 150 \mu$m). Numerical simulation of $c$-Ceff (to be shown elsewhere) under the new CCM protocol shows a stronger correlation with the measured data of Wernli et al. than the simple protocol (with Fdrop = 0) or Dresden protocol (with Fdrop > 5). The Figure shows an example of $c$-Ceff for various
UV intensities of 3 to 45 mW/cm², with $F_{\text{drop}} = (1, 2, 3, 4)$, where all cases have efficacy above the threshold value 80% within the anterior stroma crosslinked depth range of 0 to 200 μm. In comparison, curves in the range 400 to 500 μm are associated with the situation of $F_{\text{drop}} = 0$, which shows low efficacy < 80% for high intensity with $I_0 > 18$ mW/cm², where diffusion depth $D = 500, 200, 150, $ and 150 μm were used for $F_{\text{drop}} = 1, 2, 3$, and 4. The cutoff (or maximum) intensity with $c\cdot C_{\text{eff}} < 80\%$ (within 0–200 μm stroma) predicted by the $S$-formula is approximately 45 to 55 mW/cm², consistent with the clinical data of Wernli et al. The above formulas also demonstrate that not only crosslink depth (z$^*$ > 150 μm) but also crosslink strength ($S^* > 1.6$, or $c\cdot C_{\text{eff}} > 0.8$) is required in order to achieve high crosslinked stroma volume which is proportional to (z$^*S^*$), as also suggested by Bekesi et al.

To conclude, the theoretically proposed CCM using an accelerated CXL while keeping efficacy similar to that of the conventional CXL requires much more basic clinical study to validate the multiple factors influencing the CXL efficacy, including $C_0$, $F$, $I_0$, $D$, and $F_{\text{drop}}$, and the associated cutoff maximum intensity ($I^*$) and minimum exposure time ($T^*$), as shown by the $S$ and z$^*$ formulas for type I CXL. Greater details of photochemical kinetics of type II CXL and its influencing factors of efficacy, such as oxygen environment and the generation of reactive oxygen species (ROS), were shown elsewhere. Many debating issues about the CXL efficacy, such as pulsing versus continuous wave operation, accelerated versus conventional CXL, the minimum corneal thickness, and the role of oxygen in types I and II CXL require further clinical studies, although they have been partially resolved theoretically.

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References

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