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Short Communication

Recent Progress of Corneal Collagen Crosslinking (CXL) and New Potential Applications Using Combined Technology

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Introduction

Corneal collagen crosslinking (CXL) using UVA light (at 365 nm) and riboflavin (RF) solution as the photoinitiator to increase the corneal biomechanical strength or generation of free radicals to cure corneal infections, a procedure proposed by Spoerl., *et al*. in 1998 [1]. The standard Dresden (SD) protocol was proposed (in 2003) by Wollensak., *et al*. [2], in which a UVA light intensity of 3.0 mW/cm^2 was applied to the cornea for an irradiation time of 30 minutes, delivering a light fluence (dose) of 5.4 J/cm^2. To shorten the irradiation time of the SD protocol, accelerated CXL (ACX) was also developed based on Bunsen and Roscoe law (BRL) [3], leading to the ACX protocol given by light intensity of I= (3,9,18,30,45) mW/cm^2, with the associated irradiation time is inverse proportional to the light intensity given by t= (30,10,5,3,2) minutes [4]. The conventional SD protocol requires a minimum (safety) corneal thickness of 400um and a light dose of 5.4 J/cm^2. This is an Editorial short-review focusing on the most recent developments.

Recent progress

In the recent years, basic kinetic studies and new protocols have been developed to improve the efficacy of the conventional SD. They are summarized as follows.

- Strategies for improved CXL efficacy include: using higher RF concentration of 0.25% to 0.35% (vs. 0.1%); replacing the CW light by a pulsed-light [6]; external oxygen supply for enhanced type-II CXL [6]; using diffusion-enhancing device Iontophoresis [7]; and using controlled RF concentration method (CCM) during the UV irradiation [8].
- Validation BRL and the protocols for ACX, in which new efficacy scaling law was developed by Lin [5], a nonlinear law replacing the linear law based on BRL.
- New criteria for minimum corneal thickness (Z*), in which thin corneas (214 to 398 um) was clinically reported by Hafez., *et al*. [9]; analytic formula for Z* was also developed [5].
- Non UV-light, such as visible (at 660 nm) and near infrared at (750 to 980 nm) using various photosensitizers such as Rose Bengal (rather than RF) could be developed for safer and better penetration of light.

The kinetics of CXL

The basic Kinetics of CXL was developed by Lin [5] governed by the following equation for the concentration of the stroma collagen substrate

$$\frac{d[A]}{dt} = -(K_3T + K_1R + K_2S)[A]$$

Eq. (1) includes three crosslink pathways: (i) the type-I direct coupling of the triplet exited state of RF (T) and the substrate [A]; (ii) and the coupling of the radical (R) and [A]; and (iii) the oxygen-mediated type-II due to the singlet oxygen (S) coupling with [A]. Both type-I and type-II pathway can occur simultaneously, and the ratio between these processes depends on the type of photosensitizers (PS) used, the concentrations of PS, substrate and oxygen, the kinetic rates involved in the process, and the light intensity, dose, PS depletion rate etc. Solving the above kinetic equation, one may calculate the CXL efficacy defined by CE= 1- [A]/A0, with A0 being the initial concentration of the stroma substrate.

Important CXL features

Factors influencing the CXL efficacy include: UV-A light intensity, dose, exposure time, mode of exposure (pulsed or CW), riboflavin concentration, diffusion and drops pre-operation and interoperation administration, the concentration of oxygen in the stromal tissue (pre-op and inter-op), and environmental conditions. The length of the riboflavin presoaking time and viscosity of the riboflavin film also affect the crosslink depth. From the analytic formulas of Lin [5], the key features of type-I and type-II CXL are summarized and compared as follows.

- Type-I and type-II coexist in CXL, in the presence of oxygen. However, there is no type-II when oxygen is depleted or in a condition without oxygen. Type-II CXL is oxygen mediated with efficacy proportional to the light dose and oxygen and RF concentrations.
- Type-I CXL has two case: (i) unimolecular termination having efficacy is a linear increasing function of efficacy function F= bIgC/G, where b is an effective absorption constant, I is a light intensity and C is RF concentration; case (ii) for bimolecular termination, R is a proportional to the square-root function of F-function.
- Wernli., *et al*. [10] reported a sudden efficacy decrease at high light intensity (about 65 mW/cm^2), which was also predicted by Lin's formulas [5] that the steady-state efficacy is a decreasing function of light intensity, and a sudden drop is expected when the efficacy is below an efficacy threshold. This feature also predicts a fastest CXL procedure is about 90 seconds using a light intensity about 65 mW/cm^2.
- For high CXL efficacy sufficient pre-operation and interoperation administration of RF are required, such that the RF initial diffusion depth is at least 200 um in the stroma and the RF depletion could be compensated by the proposed CCM [6].

New applications

Potential new applications are under developing using the combined methods of CXL and others, including:

- Lasik-extra: Combining CXL and Lasik for thin corneas and/or high myopia correction and stopping progression of ectasia
- SMILE-extra: Combining CXL and picosecond SMILE.
- CXL combined with Intra-corneal ring segment (ICRS) implantation.
- CXL for the correction of low myopia (about 2 diopters), without the need of Lasik.
- For young myopia correction using combined CXL and orthokeratology lens (OK-lens).
- Corneal infection treated by oxygen-enhanced CXL using singlet oxygen free radicals.
- Scleral CXL for axial myopia using fiber-delivered blue light (at 445 nm) to mechanically reinforce the sclera may prevent progression in such cases [11].
- CXL for post-operative stable outcomes (or reduced regressions) in laser hyperopia correction (using a thermal diode laser), and laser presbyopia correction (using mid-IR laser).

Conclusion

CXL offers potential new applications when it is combined with other technology/methods. However, further studies are required for long-term efficacy. In addition, many of the basic kinetics and controversial issues remained to be resolved for further breakthrough of CXL and optimal protocols. Greater details are cited in the References.

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