Opinion

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Photodynamics of Corneal Collagen Crosslinking Using UVA- Light Activated Riboflavin

Jui-Teng L

Department of Biomedical Imaging and Radiological Science, New Vision Inc, Taipei, Taiwan

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Corresponding author:
Dr. Jui-Teng Lin

jtlin55@gmail.com

New Vision Inc, Taipei, Taiwan.

Tel: 886422053366

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Photodynamic therapy (PDT)

PDT is a procedure using light (often low-power laser light or LED) absorption by the external chemical agents (or photosensitizers) causing photo-chemical reactions in the treated tissues. Many photosensitizers have been developed to match the absorption peaks of light wavelengths ranging from ultraviolet (300-390 nm), visible (400-700 nm) to near-IR (700-950 nm) for applications such as in dentistry, dermatology, ophthalmology and cancer treatments in various parts of human body [1].

PDT further involves two photochemical reactions: (a) type-I reaction, where the light-excited photosensitizer covalently bonds to a constituent molecule of the cell; it is the major path for biomechanical stiffening; and (b) type-II reaction, the excited state of the photosensitizer produces a highly reactive oxygen species (ROS) such as an excited singlet oxygen, and it often involves a chain reaction; type II is the major path for cancer cell damage or bacteria's killing. In the following discussion, we will focus on one of the most important PDT, corneal collagen cross linking (CXL).

The technique of CXL using UVA light (at 365 nm) to activate riboflavin was first initiated by Seiler and Spoerl in 1998 at The University Clinic of Dresden and was approved by FDA in US in April, 2016. CXL has been developed for the treatment of corneal diseases such as keratoconus, post-LASIK ectasia, infectious keratitis and corneal melts [2].

Safety issues of CXL

The safety and efficacy of CXL are characterized by the collective parameters of [*E, I, t, A, z, D, C, q*]; where *E and I* are the UV light energy dose (fluence) and intensity, *t* is the exposure time; A and D are the absorption coefficients and diffusion depth of riboflavin (RF) in the stroma having an initial concentration *C; z* is the depth in the stroma (or corneal thickness); and *q* is the polymerization quantum efficient. *A* is further defined by *A=(a+b) C + Q,* with a and b are the extinction coefficients of the RF and the photolysis product, and *Q* is the absorption constant of stroma (without RF).

The conventional safety criteria of dose <5.4 J/cm^2 and minimum corneal thickness of 400 µm is a debating issue. The new criteria have a much wider corneal safety range of 250 µm to 400 µm depending on the UV light dose (3.0 to 10.0) J/cm^2 and the riboflavin concentration (0.1 % to 0.25%). Moreover, the reported conventional damage threshold of the endothelial cell 0.65 was at least two times underestimated [2-5].

The non-linear law

The classical Bunsen-Roscoe law (BRL) proposed that a photochemical reaction will stay constant if the total energy (or dose) is constant [2]. The accelerated CXL uses a higher UV intensity (for a fixed energy or dose) to reduce the UV exposure time (t) and a shortened irradiation time at higher irradiance should lead to the same increase in biomechanical stiffness as a longer irradiation time at lower irradiance. For examples: t= (30, 10, 5, 3, 2) minutes, for UV intensity I_0= (3, 9, 18, 30, 45) J/cm^2 based on BRL. It has been shown in ex vivo experiments that the biomechanical stiffening effect of the corneal tissue is equivalent with 10 mW/cm^2 (exposure time 9 minutes) to the standard protocol of 3 mW/m^2 (exposure time 3 minutes) [2]. However, it was also reported that the BRL is only valid for a certain range and how large this range is for corneal cross-linking remains unknown [3].

Modern theory based on nonlinear law (NLL) was recently developed [4]. The NLL shows that (for the same dose), higher intensity (with shorter exposure time) performs lower CXL efficacy. Therefore, higher dose is required in high intensity in order to achieve the same efficacy as that of low intensity. A scaling law is then proposed as follows: [exposure time] = [UV light intensity]$^{-m}$ with m=1 for BRL, and m<1.0 for NLL, with a typical value of m=0.75 was proposed by Lin [4].

Maximal efficacy

CXL efficacy may be described by either the measured demarcation line depth or by the increase in stiffness of the crosslinked collagen. For efficient CXL, one would require a crosslinking depth in the range from 150 to 300 µm, and the corresponding UV light dose ranges from 4.0 to 8.0 J/cm^2.

To improve the CXL efficacy, various techniques have been proposed. These include: pulsed mode operation of the UV light, extra oxygen supply to the corneal surface; and enhancement of the riboflavin diffusion such as diffusion in the de-epithelialized stroma (standard method); diffusion through the epithelium into the stroma (transepithelial method); or direct introduction of riboflavin into the stroma (pocket technique, ring technique, needle technique); and enrichment of riboflavin in the stroma by iontophoresis [2]. In addition to UVA light activated riboflavin, other photosensitizers using blue light (at 430 nm) and green light (at 532 nm) were also proposed.

Detailed photochemical kinetics of CXL was reported showing the roles of oxygen in both type-I and type-II reactions [5]. In addition, combination of supplemental oxygen and pulsing UV exposure providing substantial improvement of CXL efficacy was also reported by Muller et al. (Avedro Report).

To conclude, the conventional protocols of CXL based on BRL require revision based on nonlinear law which, however, requires further basic studies on the CXL photochemical kinetics and more clinical investigations to resolve some of the debating issues.

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