Original research article

Photochemical Kinetic Modeling for Oxygen-enhanced UV-light-activated Corneal Collagen Crosslinking

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ABSTRACT

Aims: To derive analytic formulas for the efficacy of type-II corneal collagen crosslinking (CXL) based on coupled macroscopic kinetic equations with an emphasis on the role of oxygen.

Study design: modeling and analysis of type-II CXL

Place and Duration of Study: Taipei, Taiwan, between Feb. and June 2017.

Methodology: Coupled macroscopic kinetic equations are derived under the quasi-steady state condition. For type-I CXL, the riboflavin triplet state [RF_3] interacts directly with the stroma collagen substrate for crosslinking. For type-II process, [RF_3] interacts with the ground-state oxygen [O_2] to form a reactive oxygen singlet (ROS) which can relax to [O_2], or interact with the extracellular matrix for crosslinking.

Results: Both type-I and type-II efficacy are nonlinear increasing function of the UV light dose (or fluence). Oxygen is required for type-II CXL, but not absolutely needed in type-I CXL. With the presence of oxygen external source, the steady-state type-II efficacy is a decreasing function of the UV intensity (for the same dose), same as that of type-I. Sufficient external oxygen supply, either pre-CXL or during CXL, will enhance the CXL overall efficacy. UV light in pulsing-mode may also improve the efficacy, but only when UV-off period is long enough for oxygen replenishment. Thin cornea (under the safety thickness criteria), low UV intensity (3 to 18 mW/cm^2), and epi-off CXL will achieve higher overall efficacy than that of thick corneas, or epi-on CXL under high intensity (>18 mW/cm^2).

Conclusion: We have derived analytic formulas for the efficacy of type-I and type-II CXL. The overall CXL efficacy is proportional to the UV light dose (or fluence), the riboflavin and oxygen initial concentration and their diffusion depths in the stroma.

Keywords: Corneal crosslinking; corneal keratoconus; efficacy; kinetic modeling; oxygen; riboflavin; ultraviolet light; photodynamic therapy.

1. INTRODUCTION

Photochemical kinetics of corneal collagen crosslinking (CXL) and the biomechanical properties of corneal tissue after CXL are reported [1]. However, much less efforts

have been invested in basic theoretical studies of photopolymerization [2-13], where Lin et al presented the first dynamic modeling for the safety of CXL [2,3]. The safety and efficacy issues of CXL have been reported theoretically [4-6]. The critical parameters influencing the efficacy of CXL include: initial concentration and diffusion depth of the riboflavin (RF) (for type-I CXL) and the oxygen (for type-II CXL), the quantum yield, the UV light intensity, dose and irradiation duration.

It has been reported that oxygen concentration in the cornea is modulated by UV irradiance and temperature and quickly decreases at the beginning of UV light exposure [9,14]. The oxygen concentration tends to deplete within about 10-15 seconds for irradiance of 3 mW/cm^2 and within about 3-5 seconds for irradiance of 30 mW/cm^2 [9]. By using pulsed UV light of a specific duty cycle, frequency, and irradiance, input from both Type I and Type II photochemical kinetic mechanisms may be optimized to achieve the greatest amount of photochemical efficiency. The rate of reactions may either be increased or decreased by regulating one of the parameters such as the irradiance, the dose, the on/off duty cycle, riboflavin concentration, soak time, and others [1,9].

The prior works of Zhu et al [7,8], Schumacher et al [9,10], and Kling [13] assumed a constant UV light intensity and ignoring the RF depletion based on the conventional Beer-Lambert law, underestimated the UV light intensity in the stroma during the CXL. The prior work also assumed a flat RF concentration and ignored the absorption of the photolytic products. Our model will remove all the above described oversimplified assumptions for a much more realistic and accurate prediction of the key parameters influencing the CXL efficacy. A generalized, time-dependent Beer-Lambert law is employed to solve the dynamic UV light intensity [4,6]. The type-I efficacy (without oxygen) has been reported by Lin et al [4,6], this study will focus on the oxygen-enhanced type-II efficacy

2. MATERIAL AND METHODS

2.1 The Modeling System

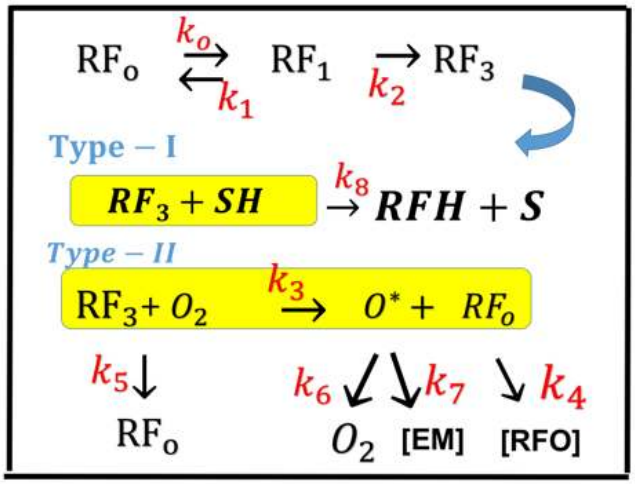

Fig. 1. The kinetics of CXL. The ground state RF molecules [RF_0] is excited by the UV light to singlet excited state (RF_1), and then triplet excited state (RF_3); in type-I, RF_3 interacts directly with the collagen substrate (SH), where as in type-II, RF_3 interacts with the ground oxygen (O_2) to form a reactive oxygen singlet (O*).

As shown in Fig. 1, the CXL process is described as follows. The ground state RF molecules is excited by the UV light to its singlet excited state (RF_1), which could be relaxed to its ground state or to a triplet excited state (RF_3). In type-I process, (RF_3) interacts directly with the stroma collagen substrate [SH] for crosslinking. For type-II process, (RF_3) interacts with the ground oxygen [O_2] to form a reactive oxygen singlet (ROS), [O*]. The ROS could be relaxed to its ground state oxygen [O_2], or interacts with the extracellular matrix (EM) to kill bacterial (to treat corneal ulcers) or to form cross linking.

The kinetic equations for the concentration of various components are shown by using short-hand notations: C(z,t) and C*(z,t) for the RF ground and singlet state [RF_0] and [RF_1]; X(z,t) and X*(z,t) for the ground state [O_2] and singlet oxygen [O*], T(z,t) for the RF triplet state of [Rf*], and [EM] for the available extracellular matrix; given by [6-9]

$$\frac{\partial C(z,t)}{\partial t} = -k_0 C + k_1 C^* + k_3 XT - k_4 X^* C + k_5 T \qquad (1.a)$$

$$\frac{\partial C^*(z,t)}{\partial t} = k_0 C - k_1 C^* - k_2 C^* \qquad (1.b)$$

$$\frac{\partial T(z,t)}{\partial t} = k_2 C^* - (k_8 [SH] + k_3 X + k_5) T \qquad (1.c)$$

$$\frac{\partial X(z,t)}{\partial t} = P_0 - P_1 \qquad (1.d)$$

$$\frac{\partial X^*(z,t)}{\partial t} = P_1 - k_4 X^* C - k_7 [EM] X^* \qquad (1.e)$$

$$\frac{\partial [EM\}}{\partial t} = -k_7 X^* [EM] \qquad (1.f)$$

where

$$P_1 = a' I(z,t) k_3 XT - k_6 X^* \qquad (1.g)$$

And the UV light intensity is given by

$$\frac{\partial I(z,t)}{\partial z} = -A(z,t) I(z,t) \qquad (2.a)$$

$$A(z,t) = 2.3[(\varepsilon_1 - \varepsilon_2) C(z,t) + \varepsilon_2 C_0 F(z) + Q] \qquad (2.b)$$

a'=83.6pε_1 λ, with p being the type-I quantum yield and λ being the UV light wavelength.; ε_1 and ε_2 are the extinction coefficients of RF and the photolysis product, respectively; Q is the absorption coefficient of the stroma at the UV wavelength. Eq. (1.c) includes one extra term, k_8[SH], for the reduction of the triplet RF due to its direct coupling to the collagen substrate [SH], when type-I process occurs simultaneously with type-II. This extra RF depletion term was ignored in previous modeling [7,8,13]. In Eq.(5.d) for the oxygen concentration, we have included a source term (P_0) to count for the situation when there is an external continuing supply, or nature replenishment, besides the initial oxygen in the stroma, which will be defined by a diffusion function later. In general, P_0 is time-dependent and can be positive or negative [7,8].

Time integration of the singlet oxygen concentration, or Eq. (1.f), efficacy of the type-II cross linking given by the time integration of the singlet oxygen concentration. The normalized efficacy of type-II cross linking defined by Ceff =1-[EM]/$[EM]_0$ = 1-exp(-S), with S-function given by [7,8]

$$S = k_7 [A] \int_0^t X^* \, dt \qquad (3)$$

In the above described CXL model, the UV light intensity in the corneal stroma is given by a time-dependent Beer-Lambert law [2,4,6]

$$I(z,t) = I_0 \exp\left[-\int_0^z A(z',t) dz'\right] \qquad (4)$$

where the time-dependent extinction coefficient A(t) shows the dynamic feature of the UV light absorption due to the RF concentration depletion. Without the RF, A(t) becomes a constant given by the absorption coefficient of the corneal stroma tissue

reported to be A=2.3Q, with Q=13.9 (1/cm). With the RF in the stroma, the initial (at t=0) overall absorption has an extra absorption defined by the extinction coefficient and initial concentration of the RF, i.e., $A(z,t=0)=A_1=2.3\ (Q+\varepsilon_1 C_0)$, with the reported data [6,9] $\varepsilon_1 = 204\ (\%\cdot cm)^{-1}$. For t>0, A(t) is an increasing function due to the deletion of RF in time and defined by both the extinction coefficient of the RF(ε_1) and its photolysis product (ε_2), where ε_2 is not yet available for human, but was estimated to be about 50 to 120 $(\%\cdot cm)^{-1}$, based on measured data in RF solution under UV light irradiation[2,3]. The steady state light intensity is given by the steady state absorption of $A(z)=A_2= 2.3\ (Q+\varepsilon_2 C_0)$. We have previously derived the effective intensity by its mean value suing $A(z,t) = 0.5\ (A_1 + A_2)$, or using a numerically fit $A(z,t)=2.3\ (Q+m\ \varepsilon_2 C_0)$, with fit parameter m=1.2 to 1.5 for ε_2 is 50 to 120 $(\%\cdot cm)^{-1}$. These methods provide us analytic formulas for the efficacy in type-I CXL [4,6]. Similar approaches maybe used for type-II CXL as follows.

The kinetic equations (1) and (2) may be numerically calculated to find the CXL efficacy, which however is too complex for us to analyze the roles of each of the parameters. For comprehensive modeling we will use the so-called quasi-steady state assumption described as follows. The life time of the singlet and triplet states of photosensitizer (C* and T) and the singlet oxygen (X*) are very short (ns to μs time scale) since they either decay or react with cellular matrix immediately after they are created. Thus, it is reasonable is to set the time dependences, dC*/dt=dT/dt=dX*/dt=0, or the quasi-steady-state conditions introduced by Zhu et al. [7,8] in a different medical system. These conditions lead to the macroscopic kinetic equation for the concentration of the ground state RF, C(z,t) and the ground state oxygen, X(z,t), as follows.

$$\frac{\partial C(z,t)}{\partial t} = -KI(z,t)[f + qG(z,t)]C(z,t) \qquad (5.a)$$

$$\frac{\partial X}{\partial t} = -bKI(z,t)G(z,t) + P_0 \qquad (5.b)$$

$$\frac{\partial I(z,t)}{\partial z} = -A(z,t)I(z,t) \qquad (5.c)$$

$$G(z,t) = C(z,t)X(z,t)/[X(z,t) + k] \qquad (5.d)$$

where $K = 83.6\,\varepsilon_1\,\lambda\,p$; λ is the UV light wavelength; p and q are the type-I and type-II quantum yield, respectively, given by $p= k_2/(k_1+k_2)$ and $q = k_4/(k_6+k_7[EM])$; $k= k_5/k_3$, $b= k_7[EM]/ k_4$ and f= 1- g, with $g=[k_5+k_3X]/k_8[SH]$; where typical values are [7,8,9,10]: p is 0.4 to 0.8; q is 0.1 to 0.3; k is 1.0 to 3.0; and the effective factor (f) is 0.5 to 0.95.

Eq. (3) has been generalized for the situation that both type-I and type-II CXL occur. It reduces to type-I only, when q=0, or dX/dt=0, or there is no oxygen supply in the process. The effective factor, defined by f= 1- g, with g being the effective regeneration of RF ground state due to type-II and type-I. that is the RF depletion in type-I is partially compensated by type-II. Reduction of the triplet RF maybe due to its direct coupling to the collagen substrata [SH] (in type-I), or its coupling to the singlet oxygen (in type-II). In general, type-I process occurs simultaneously with type-II, then type-II is terminated at the time oxygen is completely depleted in about 15 seconds (for UV intensity of 3 mW/cm^2), and may partially recovered if the UV light is turned off for few minutes. The effective regeneration factor (f=1-g) was ignored in previous modeling [7,8,13], which results an almost constant RF concentration, since qG (about 0.01 to 0.1) is much smaller than f=1-g (about 0.5 to 0.9).

The initial concentration profiles (at t=0) of the RF and oxygen may be calculated or measured based on Fick's second law of diffusion [9,10,14]. For analytic solution, we have chosen the distribution profile given by [3,6]: $F(z,D) = 1 – 0.5z/D$ for RF solution, or $C(z,t=0)=C_0F(z)$, with a diffusion depth D in the stroma; and $F'(D',z) =1 – 0.5z/D'$ for the oxygen initial concentration, or $X(z,0)= X_0F'(D',z)$, with a different diffusion depth D'. The typical diffusion depths are: D is 200 to 500 um and D' is 100 to 200 um.

The prior work of Zhu et al [7,8], Schumacher et al [9,10], and Kling [13] assumed a constant UV light intensity and ignoring the RF depletion, i.e., $X(z,t) =X_0$, is a constant in Eq. (2.b), based on the conventional Beer-Lambert law which overestimated the A(z,t) as its initial value when t>0. The prior work also assume a flat RF concentration, or F(z,t)=1 and used an oversimplified model to assume no absorption of the photolytic products, or $\varepsilon_2 =0$. The effective factor, defined by $f= 1-(k_5+k_3X)/k_8[SH]$, for the influence of type-II on the RF depletion in type-I, due to direct coupling of triplet RF to the collagen substrate [SH]. This extra RF depletion term was ignored in previous modeling [7,8,13]. Therefore, our model system based on Eq. (5) is much more accurate than the prior works in describing the CXL process when type-I and type-II coexist, specially for the initial stage prior to the oxygen depletion.

2.2 Analytic Formulas

We will first derive the analytic formulas for the efficacy of type-II CXL as follows. By approximating $G(z,t)= C(1-k/X_0)$, (for $k/X_0 <<1$) and solving for Eq. (5.a), we obtain the first-order $C^{(1)}(z,t)$ to find the solution of Eq. (5.b). Using this first order

$X^{(1)}(z,t)$ in $G(z,t) = C^{(1)}(1- k/X^{(1)})$, we find the second-order solution of Eq. (5.a) and (5.b) for the concentration of oxygen and RF

$$C(z,t) = C_0 F(z) \exp(-B't) \quad (7.a)$$

$$X(z,t) = X_0 F'(z) + P_0 t - (b' E_1/f)[\,1 + b_3\, E_{12} + b_4\, E_{23}\,] \quad (7.b)$$

$$B'(z) = B + B_1/t \quad (7.c)$$

where $E_{12} = 1-0.5\, E_2/\, E_1$, $E_{23} = 1-0.5\, E_2/\, E_1 + 0.33E_3/\, E_1$; $E_1=1-\exp(-Bt)$, $E_2=1-\exp(-2Bt)$, $B=fKI'(z)$, $B_1=(kk'C_0F-k'')E_1+k"t$, $b'=b(k'/f)C_0F(z)$, $k'= 1-k/(X_0F'(z))$, $k= k_5/k_3$; $b_3=kb/[k'(X_0)^2]$, $k"=(k/X_0F')^2$. Where we have used the mean intensity $I'(z)=I_0\exp(-A'z)$, with A' is the fit steady-state value of A (z,t), or its mean value, $A'=0.5(A_1 + A_2)$ as defined earlier. In Eq. (7.b), the source term due to oxygen replenishment (P_0t) is proportional to the oxygen replenishment time (t) which is longer in higher intensity (for a fixed dose). Therefore higher intensity has higher oxygen replenishment than low intensity.

Therefore, the quasi-steady state of the singlet oxygen, $X^*=(KI'(z)/k_7[A])G(z,t)$, is approximated by Eq. (7) and its time integration, from Eq. (3), gives the S function $S= (X_0F'-X)$ and given by, from Eq. (7.b),

$$S = b' E_1/(bf)[\,1 + b_3\, E_{12} + b_4\, E_{23}\,] \quad (8)$$

We note that S is increased by the factor 1/f= 1+ g, with $g=(k_5+k_3X_0)/\, k_8[SH]$ being the effective regeneration of RF ground state.

Comparing to the type-II S function in Eq. (8), the type-I efficacy Ceff (I)=1-exp(-S'), with S' function given by [4,6]

$$S'(z,t) = P(z,t)\sqrt{4fK'C_0F(z)/(aI'(z))} \quad (9.a)$$

$$P(z,t) = 1 - \exp[-0.5atI'(z)] \quad (9.b)$$

where $K'=(k_p/k_t)^2$ with k_p and k_t are the rate constant for the polymer growth and termination; the effective factor, f=1 (or g=0), when type-II does not occur, or when the oxygen is completely depleted.

The type-I rate equation of conversion of monomers to polymers, or the CXL efficacy [M], is given by [6,11]

$$\frac{\partial [M](z,t)}{\partial t} = -R(z,t)[M] \quad (10.a)$$

$$R(z,t) = \sqrt{a'KC(z,t)I(z,t)} \quad (10.b)$$

and S' is given by the time integration of R(z,t).

Knowing the type-I and –II efficacy, the normalized overall CXL efficacy is given by

$$Ceff = 0.5[2- \exp(-S') – \exp(-S)] \qquad (11)$$

3. RESULTS AND DISCUSSIONS

The following calculations are based on the numerical solutions of Eq. (5) with input parameters of: p=q=0.3, f=0.9, b=150, k=1.0; initial RF concentration C_0 =0.1, oxygen concentration X_0=7.3 mg/L, for the case of P_0=0. As shown by Fig. 2, the normalized riboflavin (left) and oxygen (right) profiles at z=0 (solid curves) and 100 um (dashed curves), for UV light intensity of (3,5,10,20,30) mW/cm^2; riboflavin and oxygen initial diffusion depth (D=D'=200um). As predicted by Eq. (7.a) and (7.b), RF and oxygen concentration are decreasing functions of time and depth (z). The are also strong decreasing functions of the UV light intensity, in consistent with the clinically measured data [9,13-15]; where we have chosen the coupling constant b=150 to fit clinically reported that the oxygen concentration tends to deplete within about 10-15 seconds for irradiance of 3 mW/cm^2 and within about 3-5 seconds for irradiance of 30 mW/cm^2 [9].

The importance of oxygen diffusion depth is shown in Fig. 2 for the calculated S function for type-II CXL, on the corneal surface (z=0) and in the stroma (at z=200 um), for oxygen initial diffusion depth D'=100, 150, 200 um, for flat RF conentraion (with D=10 cm). As also predicted by Eq. (8), the efficacy is proportional to b'=b(k'/f)C_0F(z) with k'= 1-k/(X_0F'(z)), and F'(z)=1-0.5z/D', which is an increasing function of D'.

It should be noted that our modeling data has the similar trend as that of Kling [13], which, however, is not as accurate as ours due to their simplified assumption of constant RF concentration in the Beer-Lambert law, or A(z,t) in Eq. (2.b) is time-independent; also the assumption of flat RF concentration profile. The effective regeneration factor (f=1-g) was also ignored in previous modeling [7,8,13], which results an almost constant RF concentration, since qG is much smaller than f=1-g.

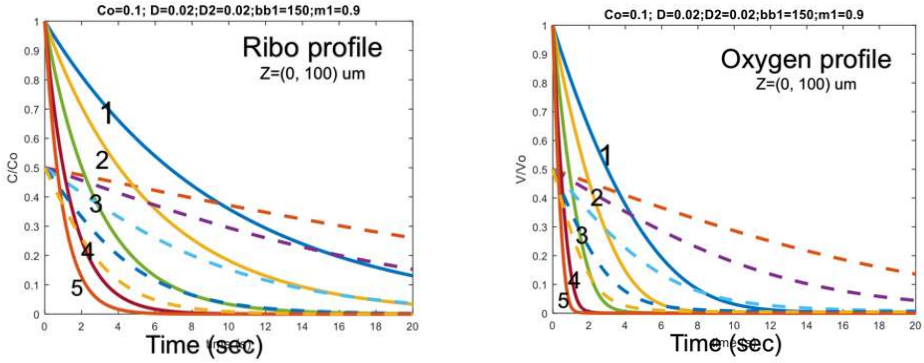

Fig. 2. The normalized riboflavin (left) and oxygen (right) profiles at z=0 (solid curves) and 100 um (dashed curves), for UV light intensity of (3,5,10,20,30) mW/cm^2 (curves 1,2,3,4,5); riboflavin and oxygen initial diffusion depth (D=D'=200um).

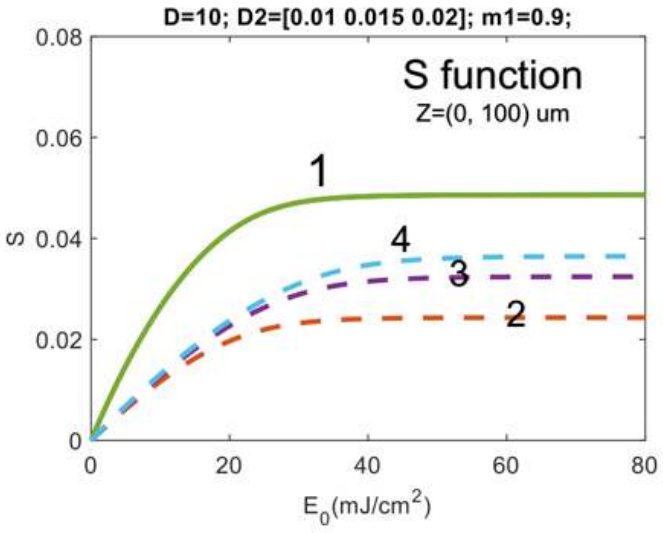

Fig. 3 The calculated S function for type-II CXL on the corneal surface (z=0, curve 1), and in the stroma (at z=200 um), for oxygen initial diffusion depth D'=100, 150, 200 um (curves 2,3,4).

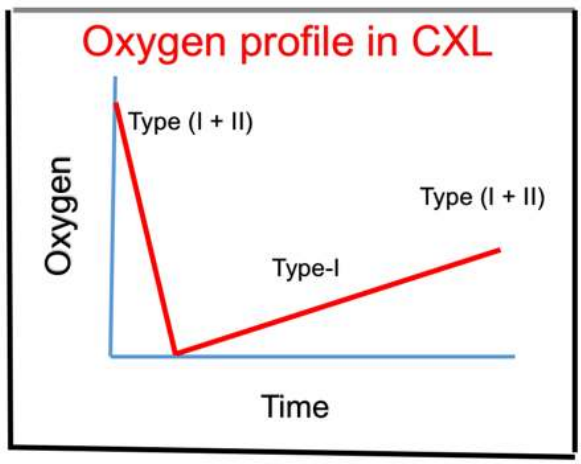

Fig. 4. Schematics of the oxygen profiles during the CXL process; in the transient stage, both type-I and –II coexist until the oxygen is depleted; then type-I dominates before the oxygen is resupplied or replenished.

From the analytic formulas Eq. (7) to Eq. (10), the key features of type-I and type-II are summarized and compared as follows:

(a) Oxygen is required for type-II CXL, but it is not required in type-I, although oxygen may also enhance slightly type-I efficacy via the the RF regeneration

factor (f=1-g). As shown by Eq. (7.b) and Eq. (8), G(z,t)=0 and S=0, when $C_0X_0FF'=0$.

(b) Both type-I and type-II efficacy are nonlinear increasing function of the UV light dose (or fluence) in the transient state. but they have different functional forms given by Eq. (8) and Eq. (9). As shown by Eq. (8), the type-II efficacy is proportional to Bt, or the UV light dose (I_0t), and the the RF and oxygen initial concentration, $C_0F(z)$ and $X_0F'(z)$. Therefore, larger diffusion depths (D or D') achieve higher efficacy in both type-I and II, as shown by Fig. 3.

(c) As shown by Fig. 4, the oxygen profiles during the CXL process. In the transient stage (about 2 to 15 seconds), both type-I and –II coexist until the oxygen is depleted; then type-I dominates before the oxygen is resupplied or replenished. Both oxygen and RF concentration is depleted by the UV light, given mainly by the effective factor (f=1-g) in Eq. (5.a) and b-factor in Eq. (5.b), whereas qG is a much small factor. The conventional assumption of a constant RF concentration in type-II is true only when it occurs alone. However, type-II process is always coupled to type-I via the effective factor (f). A complete regeneration of RF concentration (with g=1, f=0), and C(z,t) being almost a constant in the transient state, is unlikely to occur in CXL. RF depletion in type-I is partially compensated by the RF regeneration in the presence of oxygen. Typical value of f is 0.5 to 0.9, and qG is much smaller, about 0.05 to 0.1.

(d) With the presence of oxygen external source term (P_0), the steady-state type-II efficacy is a decreasing function of the UV intensity (for the same dose). This feature is the same as that of type-I, shown by Eq. (9.a). However, type-II efficacy is only governed by the UV dose, if there is no external source term (P_0).

The above described features imply that sufficient external oxygen supply, either pre-CXL or during CXL, will enhance the CXL overall efficacy. Clinically, UV light in pulsing-mode may also improve the efficacy, but only when enough UV-off period is available, about few minutes, for oxygen replenishment. Therefore, thin cornea (under the safety thickness criteria), low UV intensity (3 to 18 mW/cm^2), and epi-off CXL will achieve higher overall efficacy than that of thick corneas, or epi-on CXL under high intensity (>mW/cm^2). Administration of extra RF drop during CXL may also improve the CXL efficacy. However, there is optimal frequency (about 3 to 5 times) for the RF drops [5,6].

This study focuses on the derivation of analytic formulas and predicted features derived from them, whereas greater details of the roles of each of the components on the CXL efficacy will be shown elsewhere by numerical solution of Eq. (5), including diffusion depth (D, D'), quantum yields (p, q), effective regeneration factor (g) of RF

ground state, oxygen depletion rate (b), and the oxygen source term (P_0). The formulas developed in this study provide guidance for further clinical studies. The features predicted in this study is based on a modeling system which may not represent a real CXL system. Moreover, parameters (or the k_j values) used in the calculatuons would require further clinical measurement for more accurate values.

4. CONCLUSION

We have present the analytic formulas for type-II CXL efficacy based on coupled macroscopic kinetic equations. Oxygen is required for type-II CXL, but not absolutely needed in type-I CXL. Type-I and –II coexist in CXL process until the oxygen is depleted; then type-I dominates before the oxygen is resupplied. Both oxygen and RF concentration is depleted by the UV light, Both type-I and type-II efficacies are nonlinear increasing function of the UV light dose (or fluence), but they have different functional forms given by Eq. (8) and Eq. (9). With the presence of oxygen external source term (P_0), the steady-state type-II efficacy is a decreasing function of the UV intensity (for the same dose), same as that of type-I, The overall CXL efficacy is proportional to the UV light dose (or fluence), the RF and oxygen initial concentration and their diffusion depths.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

The author is the CEO of New Vision Inc. and has financial interest.

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