Reduced fluence corneal cross-linking in mild to moderate keratoconus: A review.

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Abstract

Keratoconus progression, especially at younger ages, is aggressive and may not stop on its own. The idea of improving biomechanical strength of the cornea to prevent disease progression and decrease its optical consequences and possibly need to corneal transplantation was a dream which almost came true. Since then, CXL has been approved by Food and Drug Administration and become a robust treatment option for progressive keratoconus as well as other conditions including post-LASIK ectasia. The chemical interaction of UVA and riboflavin is the basic principle of CXL which increases inter-fibrillar covalent bonds through photo polymerization of riboflavin and activation of oxidative pathways

Keywords: Keratoconus, Corneal cross-linking, Corneal Pachymetry, Corneal topography.

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Description

In 2003, Wollensak, et al. described corneal collagen Crosslinking (CXL) with riboflavin and Ultraviolet A (UVA) for halting keratoconus progression [1]. In 2015, the Global Consensus on Keratoconus and Ectatic Diseases also emphasized on CXL in the treatment of ectatic disorders [2]. In this way, the stiffness and rigidity of the cornea are provided. Biomechanical studies emphasized that CXL treatment should cover at least two third of the corneal stroma according to the baseline thinnest pachymetry [3,4]. CXL induced corneal stromal remodeling produce a stromal demarcation line which can be detected at examination or Anterior Segment-Optical Coherence Tomography (AS-OCT). Stromal demarcation line is usually visible in the first 3 months after CXL and its depths has been interpreted as the depth of CXL [5,6]. Confocal microscopic studies demonstrated keratocyte apoptosis or elongation, anterior to the demarcation line [7]. A global method was used to study the geometric characterisation of the cornea in disease, which must include the ultimate common pathway connecting the molecular, genetic, and environmental components that explain the pathology's genesis and progression. The condition, however, has a local origin owing to the development of structural anomalies caused by an abnormal distribution of collagen fibres in an area of the stroma and a reduction in the anchoring capacity of collagen fibrils in the Bowman layer. Repopulation of keratocytes occurs after 3 months and gradually wipes out the demarcation line.

CXL is evolving. Conventional epithelium-off CXL is called Dresden protocol and considered as the most popular regimen [1]. In this method, 3 mW/cm^2 irradiance with 370 nm UVA is applied for 30 min after removing the epithelium and saturating the cornea with iso-osmolar riboflavin [1]. There are various tomographic indicators for detecting the risk of keratoconus. When the indexes based on corneal volume are analysed, two issues arise: On the one hand, they are not very sensitive to the detection of early cases of keratoconus because the structural abnormalities are not locally defined in the primary developmental region; and on the other hand, they do not register the geometric decompensation caused by the asymmetry present during disease progression. The original Dresden protocol utilizes cumulative UVA dose of 5.4 J/cm^2. This method is time-consuming and difficult to tolerate for patients because of almost one-hour treatment time.

Literature Review

Several modifications have been proposed to improve the efficacy, safety and/or comfort of CXL. The UVA irradiation regimen is one of the modifiable factors of CXL which plays a major role. The optimal UVA regimen in keratoconic patients is still not known although previous studies showed that lower irradiance at longer time induces more stromal crosslinks [8]. However, the Bunsen-Roscoe law of reciprocity claims that a biological effect of UVA is proportional only to the total energy dose and not the time and the irradiance [9]. This is the principle of accelerated CXL in which the UVA total irradiance of 5.4 J/cm^2 is delivered in a shorter duration of time by using a higher irradiance power [10]. Therefore, the accelerated CXL regimens are considered high-irradiance protocols. Several regimens have been described for accelerated CXL considering inverse proportion between UVA intensity and illumination time: 30 mW/cm^2 for 3 minutes, 18 mW/cm^2 for 5 minutes or 9 mW/cm^2 for 10 minutes. Thus, the duration of accelerated CXL has usually decreased from one hour to 20-25 minutes. Wernli, et al. reported significant stiffening of ex vivo porcine eyes treated with total dose of 5.4 J/cm^2 and irradiances ranging from 3 to 45 mW/cm^2 [11].

Although equal photochemical effects on the cornea are expected using the accelerated CXL with the same cumulative dose, the literatures do not have consensus regarding the outcomes of accelerated regimens. Shetty, et al. highlighted that the efficiency of CXL decreases as the amount of energy increases. Therefore, the Bunsen-Roscoe law may not be applicable for CXL [12]. Similarly, some studies showed less biomechanical efficacy of accelerated CXL than conventional method in terms of corneal anatomical structure [13-15].

These studies reported demarcation line depth to be almost 100 to 200 μm shallower in accelerated method compared to conventional method with almost 300 μm stromal depths [13-15]. The oxygen in the environment is depleted rapidly at high UVA irradiances and cannot diffuse sufficiently into the cornea [8]. This could make the demarcation line more superficial and reduce the strengthening effect of accelerated protocols [16]. An ex vivo study also confirmed the trend of reduction in corneal strengthening in accelerated protocols comparing to the conventional method [17]. However, some clinical studies have revealed no clinical importance of this trend in the 10-minutes accelerated CXL method comparing to conventional one [12]. In other words, the reduction in corneal strengthening effect of CXL is not significant up to 10 minutes while more shortening of irradiation time could not have clinically acceptable outcome [12]. Mazzotta, et al. observed a mean demarcation line depth of 330 μm in 156 early keratoconic eyes underwent 9 mW/cm^2 accelerated CXL 10 minutes [18]. The long-term efficacy and safety of 10 minutes accelerated CXL protocol was similar to conventional method in this study [18].

A recent meta-analysis also reported similar stabilization of keratometry values up to 1 year after the procedure in both accelerated and conventional CXL groups despite deeper demarcation line in conventional group [19]. Two protocols (accelerated vs. conventional) can also be similar in terms of visual acuity and refraction [19]. The safety of accelerated high fluence methods has remained under question although endothelial cell damage seems to be similar between conventional and accelerated methods [19]. Beside corneal tissue itself, the unoxidized riboflavin absorbs the UVA and protects the endothelium. Because the concentration of unoxidized riboflavin is higher in conventional method comparing to accelerated, the damage to endothelium decreases in former protocol. It is also the reason for continually adding riboflavin during UVA irradiation [20].

Customized CXL are modified protocols aiming to increase the safety by shortening the UVA exposure and energy without reducing the therapeutic benefit [21]. Mazzotta, et al. proposed customizations of CXL based on corneal pachymetry to apply appropriate UVA irradiance and thus maintaining endothelial safety especially in thin corneas [22]. Similarly, the sub 400 individualized fluence CXL protocol was introduced to be performed on corneas with thickness of less than 400 μm [23]. This protocol adjusted the UV illumination time and irradiance according to the corneal thickness to achieve a safe depth of cross-linking 70 μm away from the endothelium. Indeed, endothelial toxicity determines the safety limit of UVA power and limits the use of the Bunsen-Roscoe law.

Underlying factors especially preoperative keratoconus severity seems to be predictive factors for keratoconus progression in eyes underwent CXL [24,25]. Higher maximum keratometry, higher mean keratometry, and higher Belin-Ambrósio D index at the baseline have been associated with more chance of keratoconus progression following CXL [24]. Sot, et al. also observed that patients with progression after accelerated CXL had younger age, higher maximum keratometry and more pronounced optical aberrations [25]. Therefore, some customization techniques tried to adjust the protocol of CXL according to the baseline severity and pattern of keratoconus. Customised remodelled vision protocol was one of the customized techniques based on corneal topography [26].

The UVA irradiation patterns has been individualized by corneal topography to irradiate ectatic parts of the cornea with more intense UVA irradiation whilst stronger areas are treated with little or no UVA [26]. This approach is in reverse direction of the sub400 individualized fluence CXL protocol and M nomograms of Mazotta [22,23]. While the Customised remodelled vision protocol applies more intense UVA irradiation on ectatic parts with thinner cornea, the two other protocols utilize less UVA irradiation at thinner areas to protect the endothelium. Our modification in accelerated CXL protocol was in line with the Customised remodelled vision protocol [27]. We applied low cumulative dose of UVA (3.8 J/cm^2) during accelerated CXL in corneas with mild keratoconus and observed comparable one-year results of conventional CXL protocols with cumulative dose 5.4 J/cm^2 energy [27]. It implies that, beside irradiation time and pattern, total energy of UVA can be modified to prevent unnecessary exposure of UVA in eyes with mild stages of keratectasia.

Conclusion

CXL often induces a hyperopic shift in corneas. The refractive outcome of the CXL is not predictable and various accelerated protocols despite-significant difference in flattening effect of the cornea-do not propose difference in utilized protocol based on the predicted refractive outcome. Yet, no customization has been applied based on refractive status. Customizing time, total irradiance and pattern, should be considered based on the progression probability predicted by severity of the disease and age, safety of endothelium, and refractive status of the patients.

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