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Corneal collagen cross-linking

Cross-linking do colágeno corneano

Crosslinking del colágeno corneano

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ABSTRACT

Collagen cross-linking (CXL) is the process of formation of covalent bonds within and between the collagen molecules of the corneal stroma. Studies have shown that CXL was able to stabilize keratoconus and postrefractive ectasia for a period of 1–5 years after treatment. The procedure and its technical variations are still controversial. The aim of this study was to present a review on the safety and efficacy of the most commonly used technical variations of CXL.

RESUMO

Crosslinking (CXL) é o processo de formação de ligações covalentes intra e intermoléculas do colágeno do estroma corneano. Estudos tem demonstrado que o CXL foi capaz de estabilizar o ceratocone e as ectasias pós-refrativas por um período de 1 a 5 anos após o tratamento. Controvérsias permanecem no procedimento e nas suas variações técnicas. O presente trabalho teve por objetivo revisar a segurança e eficácia das variações técnicas mais comumente utilizadas.

RESUMEN

Crosslinking (CXL) es el proceso de formación de enlaces covalentes intra e intermoléculas del colágeno del estroma corneal. Estudios han demostrado que el CXL fue capaz de estabilizar el queratocono y las ectasias post-refractivas por un período de 1 a 5 años después del tratamiento. Las controversias permanecen en el procedimiento y en sus variaciones técnicas. El presente trabajo tuvo como objetivo revisar la seguridad y eficacia de las variaciones técnicas utilizadas más comúnmente.

Keywords:
Keratoconus;
Ectasia;
Cornea;
Corneal keratocytes.

Palavras-Chave:
Ceratocone;
Ectasia;
Córnea;
Ceratócitos da córnea.

Palabras Clave:
Queratocono;
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INTRODUCTION

Collagen cross-linking (CXL) is the process of formation of covalent bonds within and between the collagen molecules of the corneal stroma[1]. This process also occurs with aging and in diabetic patients as a result of enzymatic glycation of collagen fibers[2].

The initial protocol, which was developed in Germany by researchers of the University of Dresden in 1993, includes the saturation of the corneal stroma with a photosensitizing substance, riboflavin, and its subsequent irradiation with ultraviolet-A (UV A) light at a wavelength of 365 nm[2].

Although the precise underlying mechanism is still unknown, riboflavin is thought to generate free radicals (superoxide oxygen) after irradiation with UV A light, and these radicals induce the formation of covalent bonds[3].

The Dresden protocol, which is considered to be the gold standard to which all the other variations of the technique are compared, involves removing the epithelium in the central portion of the cornea (epithelial-off or epi-off) with a diameter of 9 mm, instilling riboflavin solution (0.1% riboflavin and 20% dextran) to the corneal surface for 30 min, and irradiating it with UV A light (3 mW/cm2) for 30 min, which results in a total energy of 5.4 mJ/cm^2 [2,4].

Experimental studies have shown that corneas become more resistant after this procedure, including in enzymatic digestion tests[4]. Studies performed to evaluate the safety of this procedure showed the absence of lesions in the endothelium, lens, and retina, provided that irradiation was maintained at the same levels and the corneal stromal thickness was not less than 400 µm[5].

The first human study involved 22 patients (23 eyes) with moderate-to-severe keratoconus and showed that there was a Kmax reduction of 2 D in 16 eyes (70%) and visual acuity improvement in 15 eyes (65%)[6]. Studies with larger samples and longer follow-up periods showed that CXL was able to stabilize keratoconus and postrefractive ectasia for a period of 1–5 years after treatment[7,8,9,10,11]. This procedure and its technical variations are still controversial. The aim of this study was to present a review on the safety and efficacy of the most commonly used technical variations of CXL.

TRANSEPITHELIAL CXL

The Dresden protocol involves the removal of the epithelium to allow the penetration of riboflavin in the stroma[6]. During CXL, riboflavin diffusion is necessary to increase the efficacy of its photosensitizing activity, for the oxidation reaction, and also to avoid UV A light damage to the ocular tissues[12]. However, corneal deepithelization is responsible for most complications, such as infection, haze, and corneal opacities[13,14,15].

Studies have shown that removing the epithelium may damage the basal and stromal corneal nerves, thereby reducing corneal sensitivity[16]. The regeneration of these nerves occurs between 6 months and 1 year; however, during this period, there is a higher risk of corneal ulceration as a result of decreased sensitivity[16].

Experimental studies have demonstrated that the epithelium does not block UV A light but impairs the adequate stromal diffusion of riboflavin, thereby reducing the efficacy of CXL[12]. Agents such as benzalkonium chloride, 20% ethanol, ethylenediaminetetraacetic acid, and tetracaine have been used to loosen the tight junctions of the epithelium and allow the penetration of riboflavin[17,18]. These substances are toxic to the epithelium, and it has been shown in later studies that they did not allow an adequate stromal diffusion of riboflavin[17,18,19]. Other alternatives to avoid the removal of the epithelium include the formation of a stromal pocket using a femtosecond laser and iontophoresis[20]. The femtosecond laser creates a pocket in the stroma of a defined diameter and depth and allows the direct instillation of riboflavin into the corneal stroma[21,22]. Questions have been raised regarding the biomechanical stability of the cornea after the use of a femtosecond laser[21,22]. In iontophoresis, the application of low-gradient energy under the cornea increases molecular transportation and facilitates penetration of riboflavin, whose concentrations are however still not comparable to those obtained using the standard protocol[20]. Although transepithelial CXL is a promising method, till date no protocol has been shown to have the same efficacy as that of the standard protocol[20,21]. Recently, the absorption of an amphipathic form of riboflavin that is potentially better absorbed by the corneal epithelium has been investigated[21]. However, extending the time of exposure to this form of riboflavin did not lead to an increase in stromal saturation[21].

ACCELERATED CXL

The objective of accelerated CXL is to reduce the time of exposure to UV A light from 30 min to a few minutes[23]. This reduction in surgical time would have advantages, such as decreasing the patient's discomfort and corneal stromal dehydration[23]. This is possible by increasing the fluence but maintaining the total energy of the procedure at 5.4 mJ/cm2. Recent advances have made it possible to increase the energy to 45 mW/cm2, thereby reducing the time of exposure to UV A light to a few minutes[23].

Several studies have assessed the safety and efficacy of accelerated CXL. A retrospective study of 16 eyes treated with irradiation at 9 mW/cm2 for 10 min concluded that the keratometry and visual acuity measurements remained stable in 6–12 months of follow-up[24]. Other studies have suggested that irradiation at 7 mW/cm2 for 15 min is sufficient to avoid the progression of keratoconus[25]. However, limited data on treatment with 18 mW/cm2 for 5 min have shown good safety results but dubious efficacy[26].

Wernli et al[27] obtained equivalent biomechanical responses, which were measured by changes in the Young's modulus at 10% when comparing the standard protocol (3 mW/cm2 for 30 min) with the accelerated protocol (10 mW/cm2 for 9 min). Hammer et al.[28] found a decrease in the hardening effect with an increase in the intensity of UV A light to values above 30 mW/cm2 and by comparing the Young's moduli at 10%. In some studies, the demarcation line detected on optical coherence tomography was less dense and homogeneous and was observed in a fewer number of patients in the accelerated treatments than in the standard protocol[29].

Richoz et al. showed that a rapid depletion of oxygen occurs in 10–15 s after exposure to UV A light[30]. These authors compared irradiation with pulsed UV A light (to allow the oxygen to be replenished) for 8 min and constant UV A light for 4 min and obtained better results with the use of pulsed UV A light[30].

Hashemian et al[31] reported a smaller decrease in the density of keratocytes and less damage to the sub-basal nerves in the accelerated protocols. Ozgurhan et al[32] also observed less damage to the sub-basal nerves in the accelerated protocol. Despite these findings, protocols using high intensity of exposure to UV A light (above 30 mW/cm2) have been shown to produce variable results[29].

CXL IN CHILDREN

The most common indication of CXL in children is the treatment of keratoconus. This disease exhibits particular characteristics in children, including rapid progression of ectasia, poor adherence to the treatment, and higher incidence of complications from the treatment[33].

Keratoconus in children is significantly more severe at the time of diagnosis, with approximately 27.8% and 7.8% of children and adults with stage 4 keratoconus, respectively[34]. Moreover, disease progression occurs more rapidly in children than in adults. The reasons behind this include reduced biomechanical rigidity and the frequent coexistence of other conditions, such as eye allergies[34]. Visual impairment may be progressive and affects the social and learning development of the child[34,35]. These factors encourage researchers to assess the safety and efficacy of using CXL in pediatric patients.

In a study with a follow-up period of 4 years, patients aged less than 18 years who underwent epi-off CXL exhibited stabilization of the keratometric parameters, whereas patients aged between 18 and 39 years who underwent the same procedure exhibited decreased keratometric parameters, such as corneal flattening[36]. Although transepithelial CXL appears to be particularly useful in this population, studies have shown that it has little efficacy[37].

Chatzis et al[35] assessed patients aged between 9 and 19 years and observed that the disease progressed within a short period of time in 88% of the patients. These authors evaluated the results of epi-off CXL in this population and demonstrated a significant K_{max} reduction 2 years after treatment; however, K_{max} returned to the pre-treatment values after 3 years. They concluded that the pediatric population requires early treatment and frequent follow-up even after CXL is performed because of rapid disease progression in this group.

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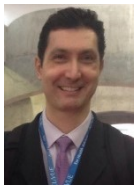

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