Editorial

Corneal Collagen Crosslinking in the Management of Keratoconus

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Keratoconus is a bilateral, non-inflammatory corneal ectasia characterised by progressive corneal thinning and bulging, leading to progressive myopia, irregular astigmatism and corneal scarring[1]. The associated irregular astigmatism and stromal scarring have a significant negative impact on the quality of life of affected patients. A conservative approach in the management of keratoconus involves spectacles and contact lenses. Surgical intervention including implantation of intra-corneal ring segments or corneal transplantation may be necessary when conservative means become intolerable or insufficient for visual needs[2]. There are still controversies in relation to the diagnosis and management of keratoconus (KCN)[3].

Corneal collagen cross linking (CXL) is a treatment option for progressive keratoconus. It utilizes ultraviolet A irradiation (UVA) and riboflavin to induce cross links within corneal stroma aiming to increase the tensile strength and stability of the cornea. The first clinical study was published in 2003 by Wollensak et al. reporting a reduction of the maximum keratometry by 2 Diopters (D) and of refractive error by 1 D in 70% of keratoconic eyes treated with CXL. It was also noted that progression was halted in all of the treated eyes[4].

It was not until recently in the USA, the Food and Drug Administration approved the treatment CXL for KCN. However, the precise definition of progression remains controversial. Most studies offered CXL to eyes when there is an increase in maximum keratometry (Kmax) of 1 Diopter or a change in either myopia or astigmatism of 1 D in 1 year[5]. Corneal thickness of less than 400µm, severe corneal scarring or ocular surface disease, prior herpetic infection and pregnancy are contraindications for CXL.

The initial clinical studies to utilize CXL in the treatment of progressive KCN employed the Dresden protocol of 3 mW/cm^2 irradiance for 30 minutes after corneal epithelial removal. It has been studied in detail and shown good results clinically and on corneal topography. Wittig-Silva et al. reported a change in Kmax by -1.03 D over 3 years, whereas Hashemi et al. reported a change in Kmax by -0.16 D over 5 years[6, 7]. The key limitation of this conservative procedure was that it took a long time for adequate treatment. To overcome this problem, accelerated CXL using a higher irradiance with a shortened treatment duration had emerged. According to the Bunsen-Roscoe law of reciprocity, having a constant radiant exposure of 5.4 J/cm^2, a higher irradiance dose should theoretically give the same treatment response. Comparative studies between conventional and various accelerated CXL protocols revealed controversial results, given the great variability of the protocols proposed[8]. Nevertheless, most studies reported the procedures to be safe to corneal endothelium.

To facilitate diffusion of riboflavin into the corneal stroma, epithelium-off CXL, which involves epithelial debridement, is performed. This may lead to perioperative pain, abnormal wound healing and rarely infectious keratitis[9]. Epithelium-on CXL was introduced as an attempt to circumvent the above. Various techniques have been employed to enhance the penetration of riboflavin through intact corneal epithelium. These include the use of topical chemical enhancers, mechanical microabrasions over the corneal epithelium and iontophoresis[10-12]. However, clinical results with most epithelium-on CXL were not as promising as epithelium-off CXL. It has been demonstrated that a higher preoperative Kmax was associated with greater corneal flattening after epithelium-on CXL in keratoconus[10].

Intra-corneal ring segments and photorefractive keratectomy have been combined with CXL aiming to provide rapid visual improvement and stabilisation of KCN progression[13,14]. More defined patient selection criteria, long-term results and standardisation of treatment protocol are still needed to support these combined treatments.

Current evidence supports the role of CXL in halting keratoconus progression, albeit the relative lack of well conducted randomised control studies[15]. Various modifications exist aiming to improve the effective and safety profile of these treatments. However, controversies remain regarding to the best timing of CXL, definition of disease progression, repeated CXL treatment, method of riboflavin administration, use of alternative chromophores, and treatment protocols. Individualisation of treatment protocol may provide the best strategies for KCN patients. Further studies are warranted to explore these fields in the future.

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