Review Article

The Use of Corneal Cross-Linking in Treatment of Progressive Keratoconus: a Review

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Abstract

Keratoconus is a common corneal ectatic disorder which affects approximately 1 in 2,000 people. The traditional treatments for keratoconus are the use of inserts, deep anterior lamellar keratoplasty (DALK) and anterior lamellar keratoplasty (ALKP). Corneal cross-Linking is a relatively new minimally invasive therapeutic approach for treatment of progressive keratoconus, which increases the structural integrity of the cornea. In corneal cross-linking the production of oxygen free radicals by ultraviolet A (UVA) light increases the biomechanical strength of cornea while riboflavin acts as a photo synthesizer for production of oxygen free radicals by UVA. Treatment of progressive keratoconus is the most widespread use of cross-linking technique. In the present manuscript we will summarize different aspects of the utilization of cross-linking in treatment of corneal keratoconus.

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Introduction

Keratoconus is a relatively common corneal ectatic disorder which affects approximately 1 in 2,000 people [1,2]. It usually develops among young adults [3]. This disease is characterized by a cone-shaped thin cornea which leads to vision impairment by causing myopia and irregular astigmatism [4,5]. The previous treatments for keratoconus were the use of inserts or corneal grafts [6] as well as deep anterior lamellar keratoplasty (DALK) and anterior lamellar keratoplasty (ALKP) [7]. In recent years, a new minimally invasive therapeutic approach, called corneal cross-linking, has been proposed for the treatment of these patients [7,8]. Early in vitro studies by Spörl et al., [9] in 1997 evaluated the potential of using a combination of riboflavin (vitamin B2) and ultraviolet type A light in treatment of keratoconus leading to advent of corneal cross-linking. Corneal cross-linking is a relatively safe procedure with minimal or no endothelial cell damage [10]. It also does not cause loss of corneal transparency or damage to deeper ocular structures [10-12]. This method is the first available therapeutic approach to increase corneal resistance, which might stop or even reverse the progression of the disease in people with keratoconus [13]. In the present manuscript we will summarize different aspects of the utilization of cross-linking in treatment of corneal keratoconus.

Mechanism of Action

Corneal collagen cross-linking is a treatment which increases the structural integrity of the cornea [14]. The production of oxygen free radicals by ultraviolet A (UVA) light in cross-linking increases the biomechanical strength of cornea and its resistance to enzymatic degradation by creating cross-links between collagen molecules in corneal stroma and strengthening the interlamellar collagen fibril adhesion of adjacent lamellae originally weakened by keratoconus [11, 15, 16]. In this process riboflavin acts as a photo synthesizer for production of oxygen free radicals by UVA and also prevents damage to deeper ocular structures by absorbing the UVA irradiation [16].

Cross-linking has a variety of other implementations like in polymer industry to increase the strength of polymers, in dentistry to increase the strength of filling material and in pathology to preserve tissue samples [17]. This process also occurs in the natural process of tissue aging, which is referred to as physiological cross-linking [18]. The cross-linking phenomenon occurs with a higher rate than normal among smokers as well as in people with diabetes mellitus, which can justify premature aging among these people [19, 20].

Indications

Treatment of progressive keratoconus is the most widespread indication of cross-linking [21]. It should be noted that documented evidence of progression of the keratoconus is necessary before performing cross-linking [22]. It can also be used in patients with post-LASIK ectasia [22], borderline endothelial function such as corneal guttata [20], as well as bullous keratopathy [23, 24] and keratectasia caused by laser in situ keratomileusis [25], pellucid marginal degeneration (PMD) and iatrogenic ectasia [26]. Corneal cross-linking has also been suggested to treat patients with infectious keratitis [27-29].

Contraindications

It was believed that corneal cross-linking should be avoided in corneas with corneal thickness of less than 400 µm [11]. Efforts have been made to modify the cross-linking procedure to be applicable in thin corneas; however the evidence of safety and efficacy in the use of modified cross-linking protocols for thinner corneas is still limited to few studies [11].

Relative contraindications are maximum K reading of more than 58.00 D [11], IOP over 21 mmhg, a history of glaucoma, corneal guttata or other endothelial irregularities, a history of recurrent erosions, ocular surface disorders, and connective tissue diseases [6]. Treatment during pregnancy should be deferred as the safety of the procedure and its impact to the fetus has not been established [12]. Another relative contraindication is extensive corneal scarring [12].

Concurrent ocular infection, neurotrophic keratopathy, past history of poor epithelial wound healing, severe dry eye, are also considered contraindication for cross-linking [12].

Complications

Permanent loss of 2 or more Snellen lines might happen in about 1 to 3 % of patients [30]. Age older than 35 years and a preoperative CDVA of better than 20/25 have been indicated as significant risk factors for complications [30]. Haze might increase immediately after cross-linking but completely subsides in most cases [31]. Temporary corneal edema and persistent corneal edema necessitating further treatment have been reported in patients undergoing corneal cross linking [32]. During the epithelial healing, the cornea is vulnerable to infection and melting and infectious keratitis has been reported [33, 34]. Also endothelial damage might occur if the cross linking procedure is used in thin corneas (340–399 μm) [35].

Outcome of CCL in some recent studies

In a study by Tiveron at al., [36] in 2017 on topographic outcomes after performing corneal cross-linking the authors found that after 3 months, steepest keratometry reading (K2) and maximum keratometry (Kmax) weresignificantly decreased with no statist cally significant difference between male and female patients. In a prospective, randomized, double-blind trial with average follow-up of 1098 days by Lang et al., [37] conducted in 2015, the efficacy and safety of corneal cross-linking for halting the progression of keratoconus were investigated. In this study, refractive power on average decreased by 0.35 ± 0.58 diopters/year in treatment group. The controls showed an increase of 0.11 ± 0.61 diopters/year [34]. The difference between the case and control group was statistically significant [37]. In a study by Recalde et al., [38] on variations in tear quantity and quality after corneal collagen cross-linking in patients with keratoconus the authors found that during the first postoperative year, corneal cross-linking does not modify the parameters used to evaluate tear film function. Plat et al., [39] in their study on influence of corneal collagen cross-linking on anterior chamber in keratoconus found that improvement of corneal parameters by corneal cross-linking in keratoconus patients have a positive effect on anterior chamber parameters at the 6-month postoperative evaluation. Kosekahya et al., [40] evaluated changes in the coordinates of the line of sight and higher order aberrations of eyes with keratoconus, following corneal crosslinking and found that line of sight significantly shifts to the nasal region after corneal corneal cross-linking in both right and left eyes and the improvements in HOAs are significant at postoperative 6th month compared to the baseline measurements. Ameen et al., [41] in a study to evaluate the efficacy and safety of transepithelial collagen cross-linking in patients with progressive keratoconus found statistically significant changes from baseline in astigmatism, Maximum simulated Keratometry value (Kmax) and Spherical equivalent (SE). They concluded that transepithelial collagen cross-linking is a safe and effective procedure with statistically significant reduction in corneal astigmatism, Kmax and SE,

with reasonable gain in Snellen's visual acuity [41]. Wittig-Silva et al., [42] in analysis of 66 progressive keratoconus patients treated with collagen cross-linking reported a flattening (K-max) by an average of 0.74 diopters at 3 months, 0.92 D at 6 months and 1.45 D at 12 months. In the control eyes, mean K-max steepened by 0.60 D after 3 months, 0.60 D after 6 months, and 1.28 D after 12 months. No statistically significant changes were found for spherical equivalent or endothelial cell density. [42] In a study performed on Iranian patients by Saffarian et al., [43] in 2010 the mean baseline simulated keratometry (SIM K) was 46.94 ± 2.37 D which decreased to 46.0 ± 2.33 D one year postoperatively.

The use of corneal cross-linking in combination with other treatment methods

Corneal cross-linking might be used in combination with other treatment modalities to optimize visual outcomes in eyes with keratoconus [44]. Combined use of cross-linking and photorefractive keratect my (PRK) has been suggested. Kymionis et al., [45] evaluated the use of customized topography-guided PRK followed by corneal CXL for treatment of progressive keratoconus. They found that at their last follow-up 16 months post operatively spherical equivalent and defocus were statistically significantly reduced to compared to pre surgical readings [45]. Fadlallah et al., [46] evaluated the safety and clinical outcome of combined photorefractive keratectomy (PRK) and corneal collagen cross-linking in treatment of mild refractive errors in patients with early stage keratoconus. They reported that UDVA significantly improved and CDVA remained stable. Also the mean spherical equivalent and the mean cylinder and mean central corneal thickness significantly decreased with no intraoperative complications [46]. Another suggested combination therapy is combined cross-linking and corneal ICRS insertion [47]. Abdelmassih et al., [48] evaluated the safety and visual outcomes of ICRS implantation followed by cross-linking in pediatric keratoconus patients. They found that ICRS implantation is a safe and effective procedure for visual rehabilitation in children with keratoconus and poor CDVA with no intraoperative or postoperative complications [48]. In this study at the 6-month follow-up, mean CDVA and UDVA showed significant improvement in comparison to preoperative levels and a significant decrease in both keratometry readings and spherical equivalent was also observed [48].

The early detection and proper management of patients with keratoconus using minimally invasive therapeutic approaches like corneal cross linking will improve the quality of life among these patients and might delay or eliminate the need for subsequent corneal transplantation [49].

Conclusion

A strong body of literature suggests that corneal cross-linking is an effective and safe treatment method for halting the progression of keratoconus. Future studies should focus on the long term results and improvements in methodology of this technique.

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Footnotes and Financial Disclosures

Conflict of Interest:

The authors declare no conflict of interest with the subject matter of the present manuscript.