Simultanaous corneal collagen crosslinking with refractive procedures: A comprehensive review

Abstract

Corneal collagen crosslinking is primarily carried out as a treatment modality for the management of corneal ectasias such as keratoconus, keratoglobus, pellucid marginal degeneration etc, as well as for the management of post refractive surgery corneal ectasias. However, it has evolved into a tool to strengthen the cornea in patients with borderline topography, who desire spectacle independence. This combined technique aims to enhance corneal strength and stability while maintaining visual acuity. However, careful patient selection, precise surgical planning, and understanding the biomechanical effects of crosslinking on the refractive outcome are essential to optimize the results. This article reviews the current evidence, risks, and considerations of simultaneous corneal collagen crosslinking and refractive surgery, highlighting its role in modern corneal and refractive surgery practices.

Introduction

Corneal refractive surgery has evolved by leaps and bounds in the past decade, thereby ushering in a new era of precision and perfection, leading to predictable and stable refractive outcomes. This can largely be attributed to thorough pre-operative screening through improved diagnostic methods, superior ablation profiles and laser beam tracking refinements.[1] This has led to more patients, choosing to undergo laser refractive correction, enabling them to lead a spectacle independent life.

However, iatrogenic corneal ectasia is a dreaded complication which can manifest many years after uneventful refractive surgery. Varying reports exist as to the incidence of this complication, which also differs depending on the procedure. The first case of iatrogenic keratectasia was

reported in 1998 by Seiler et al.,[2] who reported 3 eyes, that had undergone microkeratome assisted LASIK, which presented with rapidly progressing central steep areas 1 to 8 months after having undergone refractive surgery. Further studies have reported an incidence of 0.02% to 0.6% of post refractive surgery ectasia, which was found to be higher post-LASIK, when compared to post-PRK.[3,4]

Simultaneous corneal collagen crosslinking (CXL) was proposed as a potential method to prevent the development of iatrogenic corneal ectasia. CXL induces photopolymerization of corneal collagen fibres and leads to the formation of new covalent bonds, thereby resulting in enhanced corneal biomechanical stability.[5–7] Apart from this potential biomechanical advantage, the addition of simultaneous CXL to refractive procedures has also been shown to cause a reduction in post-operative increase in epithelial thickness,[8] which has been proposed to be a causative factor behind regression of refractive error, thereby potentially enabling long term refractive stability. Simultaneous CXL was first performed in combination with LASIK (LASIK XTRA)[5] and subsequently used in conjunction with Photorefractive Keratectomy (PRK XTRA)[9] and Small Incision Lenticule Extraction (SMILE XTRA)[10].

Combined LASIK with CXL

This approach proposes that the addition of CXL to LASIK may lead to improved corneal biomechanical stability, predictable and stable visual outcomes, more accurate refractive correction and decreased risk of regression.[11] The goal of CXL in this case is to restore the cornea to its native strength, without inducing any additional refractive changes beyond what is produced by the refractive procedure.

The soak and irradiance time of CXL in LASIK Xtra is significantly different from that used in conventional CXL. This is because of

multiple factors. It is well known that conventional CXL can induce corneal flattening to varying degrees, with a possible continued progression of the CXL effect over time.[12,13] Hence to prevent this refractive shift, the soak and irradiance times are modified to reduce the total riboflavin soaking time and decrease the total UV-A dose.[14] It is also taken into account that the time required for the riboflavin to diffuse into the target area is reduced as the riboflavin is directly applied to the corneal stroma after lifting the LASIK flap. Additionally, it has been postulated that while conventional CXL is therapeutic in in nature, aimed at strengthening an ectatic or pathological cornea, CXL when used in conjunction with LASIK is done as a prophylactic procedure with the purposing of restoring the cornea to its inherent strength and therefore, may require a lower level of irradiation.[11]

Indications

Refractive regression and iatrogenic keratectasia has been postulated to occur because of an imbalance between the biomechanical stability of the cornea and the intraocular pressure.

A paucity of literature exists on the indications of combining refractive surgery with a strengthening procedure. However, most studies have included patients with a higher risk of ectasia and regression such as those with higher levels of refractive error, thinner corneas, higher ectasia risk scores and borderline topographic parameters.[15]

Outcomes

Significantly improved post-LASIK refractive stability has been noted in both myopic and hyperopic ablations when CXL was used in conjunction with LASIK.[11] Both refractive and keratometric parameters have shown increased stability in cases where LASIK Xtra was carried out, when compared to conventional LASIK.[15] The average retreatment rate after LASIK has been reported to be around 12% the majority of which occurs in the first 2 years following the procedure.[16–18] In cases

with higher myopia, retreatment rates of up to 30% have been reported.[19,20] Therefore, it has been postulated that the addition of a strengthening procedure can result in lower retreatment rates over time.[15] Further long term follow up studies are required before definitive conclusions can be made regarding the potential ability of simultaneous crosslinking to reduce the incidence of future ectasia.

Procedure

The following protocol has been recommended by Avedro for performing LASIK Xtra[21,22]: (1) Femtosecond laser is used for the creation of LASIK flap followed by stromal ablation as is performed routinely, following which 4-5 drops of 0.22% Dextran-free riboflavin formulation (VibeX Xtra riboflavin, Avedro) are applied onto the underlying stromal bed, avoiding the flap and is left to soak for 45 to120 seconds. Subsequently, the riboflavin solution is removed through irrigation of the stromal bed with balanced salt solution and the LASIK flap is repositioned. A 375 nm UV source (Avedro KXL system, Avedro) is used to deliver UV-A radiation through the flap at a dose of 30 mW/cm^2 for 45 to 90 seconds with a total of 1.4 to 5.4J/cm2 delivered in total. While creation of the flap and stromal ablation are performed as is routine, some surgeons prefer to adjust their treatment algorithm to avoid regression.[11]

Safety and complications

Multiple studies have demonstrated the safety of this procedure.[9,10] Complications have been seen to be minimal and transient.[15] Transient lamellar haze has been reported, although not significant enough to cause a decrease in visual acuity. Other complications reported include diffuse lamellar keratitis and central toxic keratopathy.[23–25]

However, it should be noted that while combining CXL with refractive procedures may confer an additional degree of stability to the cornea,

reports of post LASIK ectasia after LASIK Xtra do exist in literature. The first such case was reported by Taneri et al.,[24] of a patient who developed post LASIK ectasia of left eye after having undergone microkeratome assisted hyperopic LASIK. Although in this case, the use of microkeratome could have potentially led to an uneven thickness of flap which could have caused the eventual weakening, it would still be wise to exercise an abundance of caution.

Combined PRK with CXL

Indications

No protocol has been established in literature as to the definitive indications of combining PRK with a strengthening procedure. A study by Sachdev et al.,[26] included patients with thinner corneal pachymetry (between 450 and 474 microns) or those with subtle changes on topography such as mild inferior–superior asymmetry or overall D value in the red zone, not amounting to forme fruste or subclinical keratoconus. The rationale of combining CXL with PRK in most published studies has been prevention of possible future regression or ectasia in patients predisposed to develop the same. Therefore, young patients, those with high myopia/hyperopia, thin corneas, along with any contributing history (such as history of allergic eye disease, eye rubbing and family history of keratoconus) have been included in most studies.[17,27–31]

Procedure

The procedure followed for PRK Xtra[26] involves transepithelial PRK photoablation followed by application of 0.1% riboflavin with

hydroxypropyl methylcellulose (Vibex Rapid, Avedro) for 90 seconds. The riboflavin is subsequently rinsed off with chilled balanced salt solution and UV-A irradiation of 30mW/cm2 is applied for a duration of 90 seconds (total energy 2.7J/cm2). This is followed by application of 0.02% mitomycin C (MMC) for 20 seconds, which is then thoroughly rinsed off with balanced salt solution. Bandage contact lens is applied.

While the above mentioned study used the PTK-PRK mode, other studies have reported the use of alcohol[32] or transepithelial PRK photoablation as well.[9,33]

Outcomes

Most studies report similar or better refractive parameters (spherical error, MRSE, UDVA and efficacy index), topographic outcomes and stability on combining PRK with CXL when compared to those undergoing CXL alone.[9,26,33]

Complications

The most common complication reported in literature following PRK combined with CXL has been the development of superficial corneal haze. The haze was seen to resolve by the 6 month follow up visit.[26] Theoretically, as well as in various existing studies, it has been seen that the combination of PRK with crosslinking may be associated with a higher tendency of haze formation, when compared to LASIK, which has been attributed to the tendency of PRK to lead to haze, in addition to the potential haze induced by crosslinking.[26,29,32,33]

Isolated reports of potentially concerning complications do exist in literature. One case of sterile marginal infiltrate was reported by Lee et al.,[9] which resolved with topical steroid therapy and did not affect final

visual outcome. One case of central toxic keratopathy has been reported by Davey et al,[25] three days after undergoing PRK with CXL.

Conclusions

The addition of strengthening procedure to LASIK or PRK has been shown to have stable refractive and keratometric outcomes, thereby establishing its safety and efficacy. However, further long-term data is required before a definitive conclusion can be drawn.

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