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Integrating Corneal Collagen Crosslinking with Refractive Procedures (LASIK and PRK): A Comprehensive Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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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

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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.

Keywords: Corneal collagen; corneal ectasias; treatment; refractive surgery.

1. 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 (Maldonado et al., 2008). 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.,(1998) 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 (Santhiago et al., 2016; Sorkin et al., 2017).

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 (Kanellopoulos and Asimellis, 2015; McCall et al., 2010; Hovakimyan et al., 2012). 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 (Kanellopoulos and Asimellis, 2014), 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) (Kanellopoulos and Asimellis, 2015) and subsequently used in conjunction with Photorefractive Keratectomy (PRK XTRA) (Lee et al., 2017) and Small Incision Lenticule Extraction (SMILE XTRA) (Ganesh and Brar, 2015). We performed this review to comprehensively compare the outcomes of refractive surgery with or without cornea collagen crosslinking.

2. METHODS

This systematic review included studies which were either observational studies or randomized controlled trials, which compared refractive surgeries(SMILE, LASIK and PRK) with and without CXL. We systematically reviewed 3 databases including PubMed, Medline and Cochrane central register of controlled trials from inception to December 2024 with the following keywords “LASIK”, “femtoLASIK”, “laser assisted in situ keratomileusis”, “PRK”, “photorefractive keratectomy”, “XTRA”, “crosslinking”, “cross linking” and “CXL”. Studies without a control group, which included patients with history of keratoconus, letters to editor and conference abstracts were not included.

3. 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 (Rajpal et al., 2015). 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 (Koller et al., 2011; Kanellopoulos and Asimellis, 2014). 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 (Wollensak et al., 2003). 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 (Rajpal et al., 2015).

3.1 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 (Lim and Lim, 2019).

3.2 Outcomes

Significantly improved post-LASIK refractive stability has been noted in both myopic and hyperopic ablations when CXL was used in conjunction with LASIK (Rajpal et al., 2015). Both refractive and keratometric parameters have shown increased stability in cases where LASIK Xtra was carried out, when compared to conventional LASIK (Lim and Lim, 2019). 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 (Yuen et al., 2010; Alio et al., 1993; Randleman et al., 2009). In cases with higher myopia, retreatment rates of up to 30% have been reported (Alio et al., 2008; Sugar et al., 2002). Therefore, it has been postulated that the addition of a strengthening procedure can result in lower retreatment rates over time (Lim and Lim, 2019). 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.

3.3 Procedure

The following protocol has been recommended by Avedro for performing LASIK Xtra (Tan et al., 2015; Avedro, 2015): (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 (Rajpal et al., 2015).

3.4 Safety and Complications

Multiple studies have demonstrated the safety of this procedure (Lee et al., 2017; Ganesh and Brar, 2015). Complications have been seen to be minimal and transient (Lim and Lim, 2019). 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 (Seiler et al., 2015; Taneri et al., 2017; Davey et al., 2017).

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., (2017) 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.

Table 1. Summarization of key studies reviewed in the article

Study	Year	Objective	Treatment Combination	Study Design	Key Findings	Outcomes Measured	Conclusions
Maldonado MJ, Nieto JC, Piñero DP	2008	Review of LASIK technologies	LASIK (no crosslinking)	Review article	Advances in LASIK technologies, including improved precision and safety.	LASIK technology evolution, precision in ablation, safety enhancements	LASIK has evolved to become a highly precise and safer procedure.
Seiler T, Koufala K, Richter G	1998	To assess the risk of keratectasia post-LASIK	LASIK alone	Retrospecti ve analysis	Iatrogenic keratectasia risk after LASIK, particularly in patients with thin corneas or high myopia.	Postoperative corneal shape, incidence of keratectasia	Keratectasia risk is significant, highlighting the need for caution in high-risk patients
Santhiago M, Giacomin N, Smadja D, Bechara S	2016	Risk factors for ectasia after refractive surgery	LASIK/PRK alone	Review article	Identified risk factors for ectasia including corneal thickness, preoperative topography, and myopia degree.	Risk factors for ectasia, corneal stability	Preoperative assessment is critical for minimizing ectasia risks.
Sorkin N, Kaiserman I, Domniz Y, et al.	2017	Risk assessment for ectasia post-PRK	PRK alone	Retrospecti ve study	Identified higher risk for ectasia in thin corneas post-PRK, emphasizing the need for additional stability measures.	Ectasia risk factors, post-PRK outcomes	Risk for ectasia post-PRK is higher than previously assumed, especially in thinner corneas.
Kanellopoulos AJ, Asimellis G	2015	Combined LASIK with prophylactic high-fluence CXL for high myopia	LASIK + High-fluence CXL	Prospective study	Found improved corneal stability and refractive outcomes with high-fluence CXL combined with LASIK for high myopia.	Visual outcomes, corneal stability, myopia correction	Combined LASIK and CXL provides enhanced safety and efficacy in high myopia cases.
McCall AS, Kraft S, Edelhauser HF, et al.	2010	Mechanisms of corneal tissue cross-linking	CXL alone	Laboratory study	Explored the biochemical mechanisms behind CXL, including riboflavin and UVA's role in strengthening corneal tissue.	Biochemical changes post-CXL, corneal collagen strengthening	Understanding the mechanisms helps optimize CXL protocols.

Study	Year	Objective	Treatment Combination	Study Design	Key Findings	Outcomes Measured	Conclusions
Hovakimyan M, Guthoff RF, Stachs O	2012	Review of current status and future of CXL	CXL alone	Review article	Reviewed the progress of CXL techniques, emphasizing the importance of improving efficacy and safety.	CXL mechanisms, treatment advancements	CXL remains a promising treatment for corneal diseases like keratoconus and post-surgical ectasia.

4. COMBINED PRK WITH CXL

4.1 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.,(2018) 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. (Alio et al., 1993; (Binder, 2007; Amoils et al., 2000; Spadea et al., 2012; Moshirfar et al., 2014; Brar et al., 2020)

4.2 Procedure

The procedure followed for PRK Xtra (Sachdev et al., 2018) 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 (Hyun et al., 2017) or transepithelial PRK photoablation as well. (Lee et al., 2017; Ohana et al., 2018)

4.3 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. (Lee et al., 2017; Sachdev et al., 2018; Ohana et al., 2018)

A study by De Rosa et al.,(2022) aimed to evaluate the effectiveness and long-term outcomes of combining photorefractive keratectomy (PRK) with corneal collagen cross-linking (CXL) in treating patients with keratoconus. The study followed patients for two years to assess visual acuity, corneal shape, and stability after the combined treatment. Results indicated that this combination led to significant improvements in both visual acuity and corneal curvature, with a stable keratometric and refractive effect over the follow-up period. The study concluded that PRK combined with CXL is a safe and effective treatment for halting the progression of keratoconus and improving visual outcomes.

4.4 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. (Sachdev et al., 2018) 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. (Sachdev et al., 2018; Spadea et al., 2012; Hyun et al., 2017; Ohana et al., 2018) Studies also report that despite producing similar keratometric and refractive outcomes, CDVA at 12 months may be inferior to isolated refractive procedures. (Wollensak et al., 2003; Randleman et al., 2009; Seiler et al., 2015; Sachdev et al., 2018 Amoils et al., 2000)

Isolated reports of potentially concerning complications do exist in literature. One case of sterile marginal infiltrate was reported by Lee et al.,(2017) 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, (2017) three days after undergoing PRK with CXL (Dal et al., 2024).

5. 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.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT

It's not applicable.

ETHICAL APPROVAL

It's not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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