

Photorefractive Keratectomy with Protection from Ablation-Induced Secondary Radiation and Cross-linking Effect

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Abstract

Purpose: To consider the benefits of photorefractive keratectomy with protection from ablation-induced secondary radiation and cross-linking effect.

Methods: Photorefractive ablation with protection from ablation-induced secondary radiation and cross-linking was performed in 248 patients on 495 eyes with myopia and myopic astigmatism of various degrees. Before photorefractive ablation, the corneal stroma was saturated with 0.25% isotonic riboflavin solution, which was applied as an aerosol using an ultrasonic nebulizer. The saturation time ranged from 2 to 10 minutes depending on the degree of myopia, the volume of corneal stroma removed and the type of operation. TransPRK, LASIK, and FemtoLASIK operations were performed on modern excimer and femtosecond ophthalmic lasers. Methods of computer keratopography, aberrometry, optical coherence tomography and densitometry were used. The observation period is from 1 month to 5 years.

Results: Riboflavin-rich corneal stroma layers worked as spectral filters and absorbed the ablation-induced secondary radiation. According to densitometry and OCT of the cornea, this was accompanied by the formation of a membrane-like structure on the ablation surface and the damped effect of an increase in optical density in the adjacent layers of the stroma. In some cases, a gentle demarcation line was observed in these layers of the corneal stroma, which confirmed the presence of a crosslinking effect. With this method of photorefractive keratectomy, the severity of the postoperative inflammatory response was reduced. Irreversible forms of subepithelial or stromal fibroplasia were noted. This made it possible to abandon the use of mitomycin-C and reduce the duration of topical use of dexamethasone. Dynamic observations showed an acceleration of stabilization of optometric and visual results in photorefractive keratectomy with pre-saturation of the corneal stroma with 0.25% isotonic riboflavin solution.

Conclusions: Photorefractive keratectomy with pre-saturation of the corneal stroma with an isotonic 0.25% riboflavin solution provides absorption of the ablation-induced secondary radiation and a cross-linking effect with the formation of a membrane-like structure on the ablation surface. This compensates or reduces the lesion of the photoprotective and strength properties of the thinned cornea, the risk of developing fibroplasia and ectasia.

Keywords: *Photorefractive Keratectomy; Ablation-Inducing Secondary Radiation; Riboflavin; Cross-Linking*

Abbreviations

PRK: Photorefractive Keratectomy; TransPRK: Transepithelial Photorefractive Keratectomy; PTK: Phototherapeutic Keratectomy; LASEK: Laser Subepithelial Keratectomy; FemtoLASIK: Femtolaser *in Situ* Keratomileusis; CXL: Collagen Cross-Linking; LASIKXtra: Laser *in Situ* Keratomileusis + Collagen Cross-Linking; FemtoLASIKXtra: FemtoLaser *in Situ* Keratomileusis + Collagen Cross-Linking; KCN: Keratoconus; UV: Ultraviolet; UV-A: Ultraviolet-A; UV-B: Ultraviolet-B; ROS: Reactive Oxygen Species; D: Diopter; OFR: Oxygen Free-Radicals; OCT: Optical Coherent Tomography

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Introduction

According to the data available in the literature during photorefractive keratectomy, part of the radiation is transformed into longer waves that penetrate much deeper than the evaporated stroma layer [1-5]. This secondary radiation causes the fluorescence of collagen proteins and has a different effects on keratocytes, nerves and the stroma layers adjacent to the ablation zone [6]. In the spectrum of secondary radiation, there are wavelengths in the range from 260 to 290 nm that have a mutagenic effect, and wavelengths in the range from 295 to 320 pass through the cornea and reach the lens [3]. The latter indicates the need to protect the cornea and lens from ablation-induced secondary radiation.

Photorefractive corneal thinning weakens protection against external UV radiation. This is one of the risk factors for cataractogenesis and earlier cataract development after laser keratorefractive surgery [7]. In addition, violated the strength properties of the cornea. To a greater degree, the biomechanics of the cornea changes after the LASIK and FemtoLASIK operations with the formation of a surface flap. So, depending on the size and thickness of the surface flap on the leg, the strength properties of the cornea are reduced by 15-35%. Subsequent photorefractive ablation further violates the biomechanical properties of the cornea after *in situ* laser keratomilelisis [8-10].

Various technologies of accelerated prophylactic crosslinking have been developed for the prevention of keratoectasis in photorefractive surgery of the cornea [9-13]. However, the feasibility of crosslinking during photorefractive operations on the cornea continues to be debated among laser refractive surgeons. This was due to the fact that the additional UV irradiation of the cornea increased the ablative oxidative stress and the aseptic inflammatory response in the early postoperative period. In some cases, accelerated cross-linking reduced the accuracy of the photorefractive effect and was accompanied by the formation of sterile infiltrates, ulcerations and opacities in the cornea [14]. That is why it is necessary to develop new approaches to crosslinking in laser refractive surgery of the cornea.

Purpose of the Study

To consider the benefits of photorefractive keratectomy with protection from ablation-induced secondary radiation and cross-linking effect.

Materials and Methods

In the clinic, photorefractive ablation with protection from ablation-induced secondary radiation and crosslinking was performed in 248 patients on 495 eyes with myopia and myopic astigmatism of various degrees. The age of patients with myopia and myopic astigmatism of varying degrees ranged from 18 to 57 years old, the average was 24.5 ± 4.7 years. The summary table presents the main characteristics of the clinical material in various operations of photorefractive ablation with riboflavin (Table 1 and 2).

Indicators	Weak myopia and myopic astigmatism	Moderate myopia and myopic astigmatism	High myopia and myopic astigmatism	Total
Men	58	30	20	108
Women	66	48	26	140
Amount of patients	124	78	46	248

Table 1: Characteristics of clinical material according to the number of patients, eyes, sex and degree of myopia.

Indicators	Weak myopia and myopic astigmatism	Moderate myopia and myopic astigmatism	High myopia and myopic astigmatism	Total
TransPRK with riboflavin	220	124	61	405
LASIK with riboflavin	10	8	10	28
FemtoLASIK with riboflavin	18	24	20	62
Amount of operations	248	156	91	495

Table 2: Characteristics of clinical material with various technologies of photorefractive ablation with riboflavin.

Before photorefractive ablation, the corneal stroma was saturated with 0.25% isotonic riboflavin solution, which was applied as an aerosol using an ultrasonic nebulizer. The saturation time ranged from 2 to 10 minutes depending on the degree of myopia, the volume of stroma removed and the type of operation. TransPRK, LASIK and FemtoLASIK operations were performed on modern excimer laser and femtosecond ophthalmic instruments. Corneal topography, aberrometry, and corneal densitometry were performed on a TMS-5 instrument (Tomey Corporation, Nagoya, Japan). OCT of the cornea on high-resolution spectral tomographs RTVue 100 and RTVue XR100 (Optovue, Fremont, USA). The observation period ranged from 1 month to 5 years.

All clinical trials were conducted in accordance with the principles of the Declaration of Helsinki. For laser photorefractive surgeries with pre-saturation of the stroma with riboflavin, an additional permit was obtained from the ethics committee of the National Medical and Surgical Center named after N.I. Pirogov, Moscow, Russia. Before the operation, each patient signed an informed consent.

Results

Riboflavin saturation of the corneal stroma did not affect the accuracy of photorefractive ablation, which was consistent with our previous experimental studies [15-17]. Analysis of the immediate results of TransPRK with stromal saturation with riboflavin showed a decrease in the level of aseptic inflammatory response and a reduction in epithelialization times by an average of 24 hours. Complete epithelialization of the ablation zone within 48 hours was noted in 94% of cases. Ablation with riboflavin improved the quality of the ablation surface. Densitometry and OCT of a biomicroscopic transparent cornea at various times after TransPRK revealed the presence of a membrane-like structure on the ablation surface and an increase in optical density in the adjacent layers of the cornea stroma (Figure 1). Membrane-like structure was detected only in cases where its thickness exceeded 5 microns. This was due to the resolution of the spectral optical tomography. Dynamic observations have shown that with TransPRK technology with pre-saturation of the corneal stroma with 0.25% isotonic riboflavin solution, the time required for stabilization of optometric and visual results is reduced by an average of 30%.

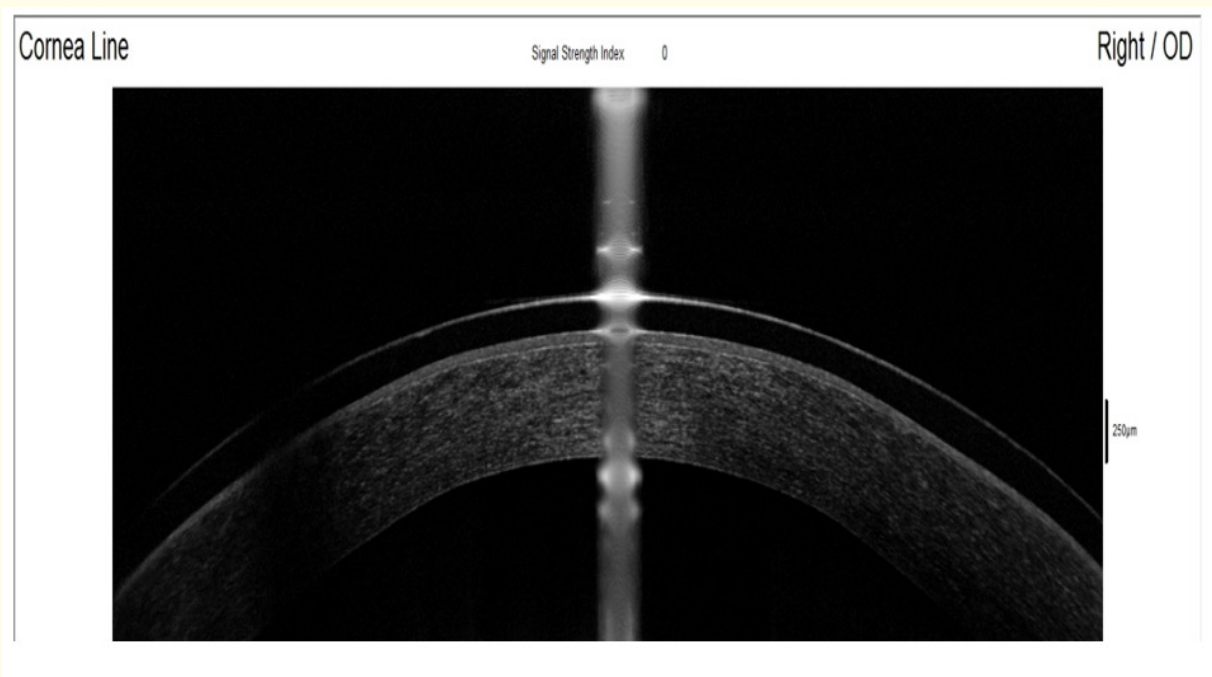


Figure1: OCT of the cornea with complete epithelization under the contact lens 48 hours after TransFRK with riboflavin. A thin membrane-like structure is visible in the ablation zone under the epithelium.

Upon photorefractive ablation with riboflavin, irreversible forms of subepithelial or stromal fibroplasia were not observed. This made it possible to abandon the use of mitomycin-C and reduce the duration of topical use of dexamethasone.

There were no significant differences between corrected visual acuity before surgery and visual acuity without correction after TransPRK with riboflavin. A more detailed analysis was presented in our previously published papers [6].

The use of special parameters of the excimer laser radiation subablation threshold mode allowed us to significantly expand the laser modification of the ablation surface and form a membrane-like structure of greater thickness on it. With this approach, according to OCT and corneal densitometry, the optical density in the layers of the corneal stroma adjacent to the membrane increased to a greater extent. Clinical observations have shown that an increase in the thickness of the membrane-like structure did not affect visual acuity (Figure 2 and 3). This approach was used by us in cases of suspected subclinical keratoconus in the eyes with axial myopia. In some cases, the TransPRK showed a gentle demarcation line, which was reversible (Figure 4).

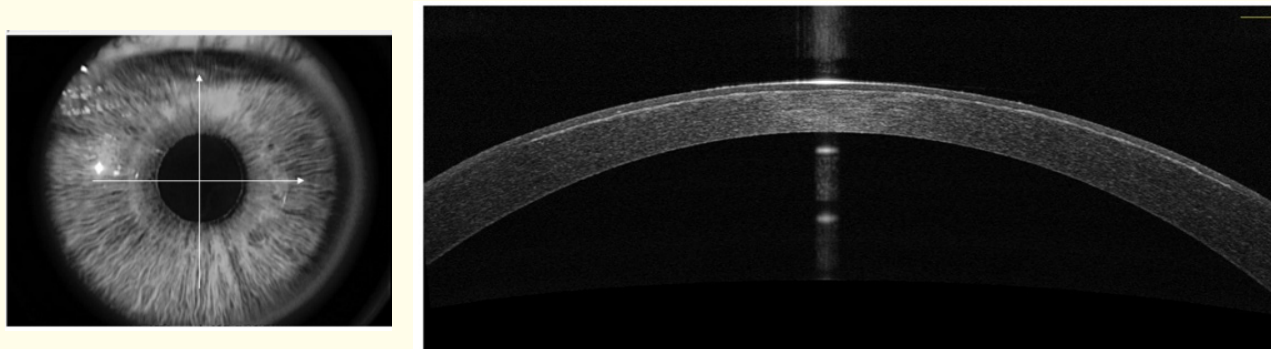


Figure 2: OCT of the cornea one month after TransPRK with riboflavin. An increase in the thickness of the membrane-like structure in the ablation zone was achieved by additional exposure to the excimer laser radiation below the ablation threshold. Visual acuity is 1,0.

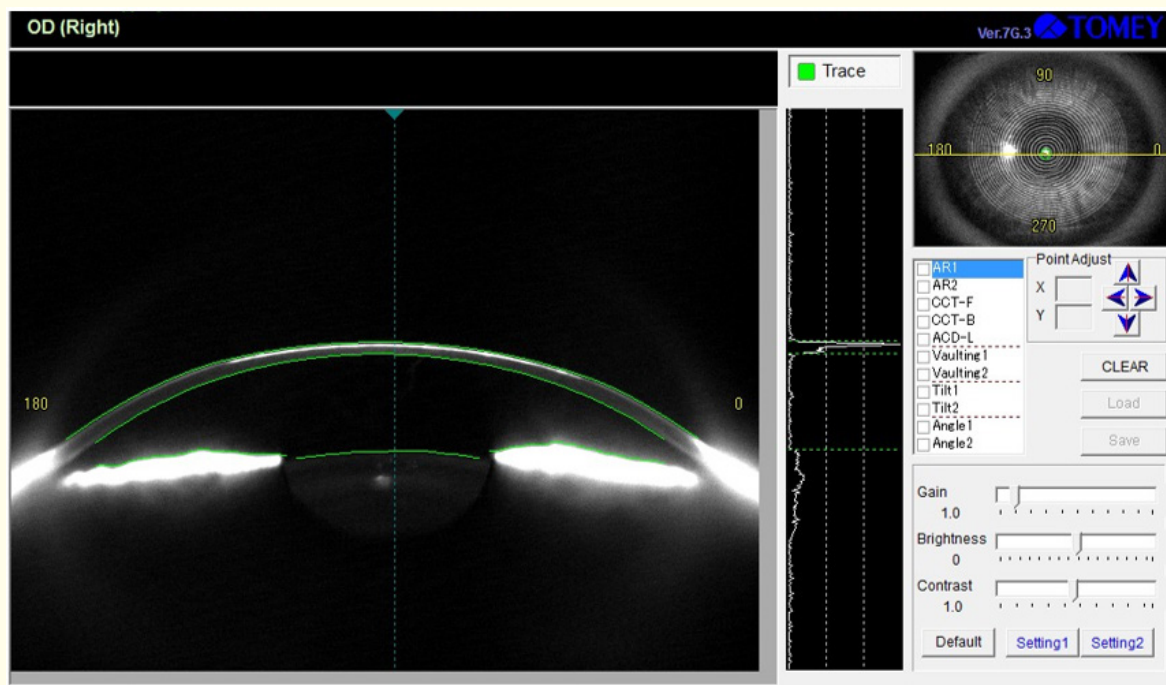


Figure 3: Densitometry of the cornea three months after TransPRK with riboflavin. An increase in the thickness of the membrane-like structure in the ablation zone was achieved by additional exposure to the excimer laser radiation below the ablation threshold. Visual acuity is 1,0.

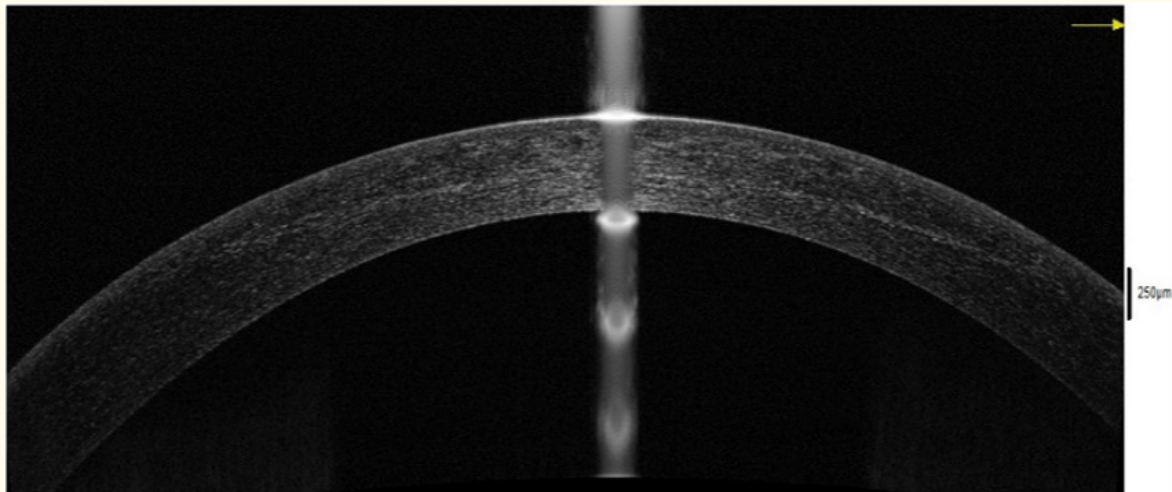


Figure 4: OCT of the cornea one month after the operation of TransPRK with riboflavin. Accordingly, the ablation zone in the stroma is determined by a demarcation line.

The LASIK and Femto-LASIK operations with pre-ablation of stroma saturation with riboflavin were not inferior to the traditional technology in terms of the accuracy of the achieved refractive effect. At the same time, due to this type of technology, a laser-induced cross-linking effect was detected. Objective confirmation of the cross-linking effect was the detection of a demarcation line of various severity 2 - 4 weeks after the operation.

The appearance of the demarcation line at different depths and its shape keeps pace with the damped absorption of secondary radiation induced by photorefractive ablation (Figure 5). No corneal complications have been identified. In our opinion, such an approach to preventive cross-linking with laser keratomileusis has advantages over LASIKXtra and FemtoLASIKXtra operations.

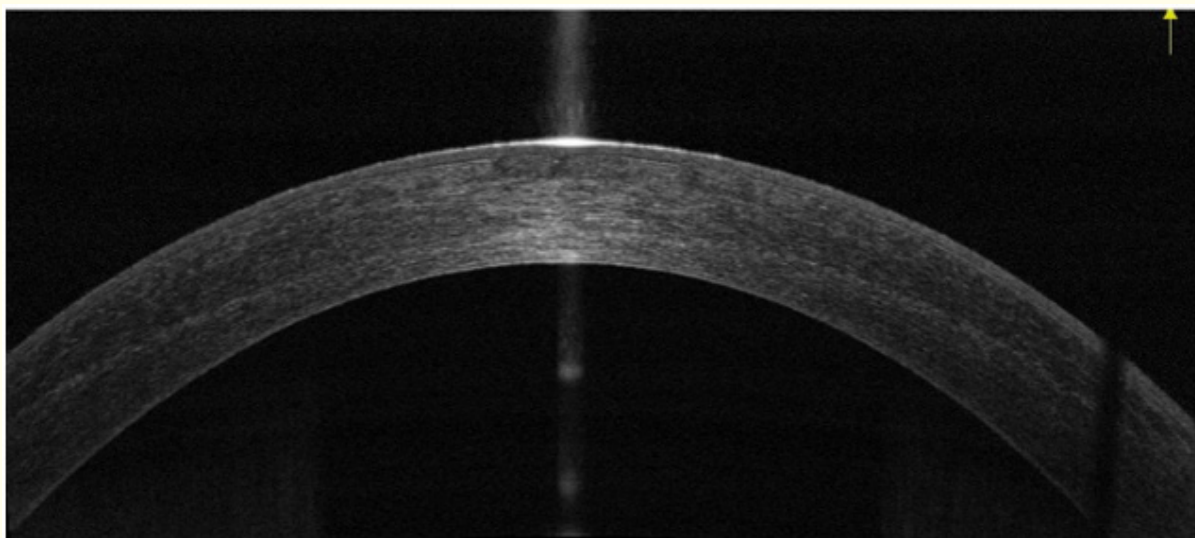


Figure 5: OCT of the cornea one month after the operation of FemtoLASIK with riboflavin. Accordingly, the ablation zone in the stroma is determined by a demarcation line.

Discussion

Aerosol irrigation with a 0.25% isotonic riboflavin solution using an ultrasonic nebulizer made it possible to intensify the saturation of the corneal stroma. The high dispersion of aerosol particles contributed to their faster and deeper penetration into the stroma of the cornea, increased their pharmacological activity. In addition, with this technology, the formation of an uneven layer of riboflavin solution on the surface of the stroma before its photorefractive ablation was excluded. The corneal stroma with riboflavin absorbed the ablation-induced secondary radiation, which weakened the irradiation of keratocytes, nerves, collagen and proteoglycan structures in the deep-lying layers of the thinned corneal stroma. This indicated the promising application of this technology in laser refractive surgery of the cornea. With this approach, the aseptic inflammatory response was reduced in the early postoperative period. The membrane-like structure on the ablation surface and the cross-linking in the adjacent layers of the cornea were considered by us as a kind of protective barrier. This barrier prevented the interaction between epithelial and stromal cytokines in the early postoperative period. This was one of the factors preventing the development of subepithelial or stromal fibroplasia. The novelty of the technology of photorefractive ablation of the cornea with preliminary saturation of the stroma with riboflavin was protected by the Russian patent for invention [18].

In previously conducted experimental studies on biomechanical testing, it was found that the effect of laser-induced crosslinking is weaker in comparison with traditional and accelerated crosslinking [15,16]. However, this effect was sufficient for preventive crosslinking in photorefractive surgery. The principal difference in photorefractive ablation of the cornea with the effect of crosslinking was the rejection of additional UV exposure of the cornea and the use of ablation-induced secondary radiation to activate riboflavin. The technology of photorefractive keratectomy with protection against ablation-induced secondary radiation and corneal crosslinking has several advantages. Wide spectrum of ablation-induced secondary radiation covered all four peaks of maximum riboflavin absorption. This increased the total extinction coefficient and the cross-linking effect [15,17,19,20]. The pulsed nature of the secondary radiation and the scanning of the surface of the cornea with a flying spot of small diameter did not violate the re-oxygenation of the corneal stroma, which facilitated cross-linking. This took into account the fact that the additional forced oxygenation of the cornea is difficult to dose, and it can reduce the effect of cross-linking [21-23].

The induced cross-linking effect of riboflavin photorefractive keratectomy can be considered as an alternative sparing variant of the traditional and accelerated corneal cross-linking in photorefractive surgery. In our clinic we still continue to optimize the technology of laser-induced cross-linking. This concerns the determination of not only the optimal pulse repetition rate, but also the local scanning frequency in the irradiated zone of the cornea. The index of the local scanning frequency reflected the frequency of a scanning laser beam at the same point in the cornea. Technologies of laser-induced cross-linking for laser modification of the ablation surface, creation of various thickness of membrane-like structure, operation LASIK and FemtoLASIK with the effect of cross-linking are patented now. These technologies will be discussed in more detail in our subsequent publications after obtaining patents for inventions.

Conclusion

Photorefractive keratectomy with pre-saturation of the corneal stroma with an isotonic 0.25% riboflavin solution provides absorption of the ablation-induced secondary radiation and a cross-linking effect with the formation of a membrane-like structure on the ablation surface. This compensates or reduces the violation of the photoprotective and strength properties of the thinned cornea, the risk of developing fibroplasia and ectasia.

Conflict of Interest

None to declare.

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