Laboratory Evaluation and first clinical case of a novel technique for myopia correction: Continuous wave laser cornea shrinkage coupled with CXL.

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Introduction

- Historical attempts (CK/LTK/MTK/DTK) at reshaping corneal collagen in order to achieve a refractive change are well-known in the industry. A particular attractiveness of these procedures has been due to a non-ablative tissue sparing reshaping result, while a notable concern has been stability/regression of effect, hence long term predictability. Recently, Avedro’s Keraflex (MTK) two step procedure was introduced, utilizing a contact probe which deposits circular patterned microwave thermal energy onto the anterior cornea inducing collagen shrinkage. However, a circular epithelial defect was noted immediate post-op by the Keraflex procedure. This thermal step is sequenced by selective (lesional) collagen cross-linking.
- Herein, we report a novel thermal reshaping application where a continuous wave mid-IR laser is used to create collagen shrinkage mid-stromally, fully sparing the corneal epithelium (and endothelium) and to a large extent, the Bowmans membrane, secondarily applying high irradiance UV light with a custom (trans-epithelial) riboflavin formulation for rapid collagen cross linking to stiffen collagen for durability/persistence of this refractive effect in a laboratory model.

Methods-Technique video

- Ten cadaver eyes, provided by the Eye Banks for Sight Restoration from New York were utilized on a KATENA single use artificial chamber. The corneas were carefully handled so as to not disturb their epithelium with instillations of Vidilac preserved artificial tears (Bausch & Lomb Dublin, Ireland). The corneas were imaged pre-TS by a corneal OCT (Optovue California, USA), a corneal topography (Oculus topography, Germany) and the Pentacam (Oculus, Germany) and a Konan ECD imager in order to establish a baseline of cornea parameters: texture and anatomy as well as cornea curvature and refractive power. Next, the corneas were placed under the prototype TS-RXL device (articulating arm).
- The TS-RXL delivery system consisted of a mid-IR (2013nm) laser, fiber coupled to a PC-controlled scanner, delivering a focused spot (~600um diameter) onto the cornea through an applanating chilled sapphire lens. The chilled lens is housed in a cone assembly on the articulating arm. The temperature of the sapphire lens was settable and was cooled to ~8^{o}C. The TS-RXL arm was lowered to applanate the cornea. During this process, the cornea under illumination was directly visualized by the operator through the superior opening of the cone; and on a PC image fed from the video camera. *see figure 1 and 2*. Ring diameters, sequence of patterns, along with speed and power were settable on the PC screen by the surgeon. Due to extensive flexibility in parameter selection (lesion depth/diameter/draw speed/sequence/opacification control), significant precision of outcomes (Diopters of correction) was provided for by the device.

Methods-2

- Following an applanated cooling period of 30 seconds, the treatment was begun under footswitch control. It should be noted that the key parameters of the laser application (power, speed, ring diameters, rings sequence) were surgeon specified at the start of each exposure. The surgeon could select one, two, three, up to seven ring applications in sequence. These rings can be placed anywhere on the applanated surface of the cornea (including selectively and precisely decentered) Intra-ring distance was set per surgeon's preference. Based on preliminary unpublished work that we have done with this device for correction of myopia, we decided to place the 3 sub-surface lesional rings at 3mm, 4mm and 5mm diameters, each ~80 um deep, centered on the cornea.
- The device was footswitch activated and each ring was created by the continuous wave laser, applying the laser energy in a circular fashion counter clockwise, to create a complete circular sub-surface annulur ring lesion. First, the 3mm diameter ring was completed, then the 4mm, and finally the 5mm ring was completed. The duration for laser application for each ring took about 4 seconds, and the total applanation duration of the lens on the cornea lasted about one minute (30 seconds chill+12 seconds Sx+15 seconds chill). The system is designed to provide constant but selectable linear draw speeds at each diameter thus inducing a uniform quality of lesion. Following IR laser delivery, the cooling continued for 15 seconds.
- Next, the applanation lens was disengaged from the cadaver cornea. The cornea was then evaluated on the slit lamp. The clinical effect of the laser treatment was clearly evident as white opaque sub-surface circular rings within the corneal stroma. There was no epithelial defect noted on the corneal surface, and the corneal shrinkage noted on the slit lamp was evaluated to be at about half the corneal depth. This was then further evaluated by corneal OCT and corneal topography and Pentacam mapping.
- The hyperopic treatment was very similar to the myopic treatment described before, with the difference being that the concentric rings were applied at 6mm, 7mm and 8mm diameters from the center of the applanated cornea.

Results

- Myopic treatment: Five corneas treated with myopic treatment revealed very similar slit lamp and corneal OCT effect. Corneal shrinkage was achieved starting at about 80um depth to extend down to about 400um depth with a maximum lesion annulus thickness of about 800um. There was no alteration or opacity in the corneal epithelium while corneal topography showed flattening of the cornea, creating a hyperopic shift, which ranged anywhere from 4 to 8 diopters with a mean change of 6.5 diopters.
- Similar results were found in the hyperopic group where the myopic shift (steepening) of the central cornea was found to be between 2 and 6 diopters, with an average of 4.2 diopter change in the central cornea.
- The representative examples from the myopic treatment and the hyperopic treatment are illustrated in figures 3 and 4. Clinical pictures of the corneas post treatment are illustrated in picture 5, as well as clinical pictures of the cornea after the collagen cross-linking and part of the procedure in picture 6, and cornea OCTs showing the corneal shrinkage are illustrated in picture 7.
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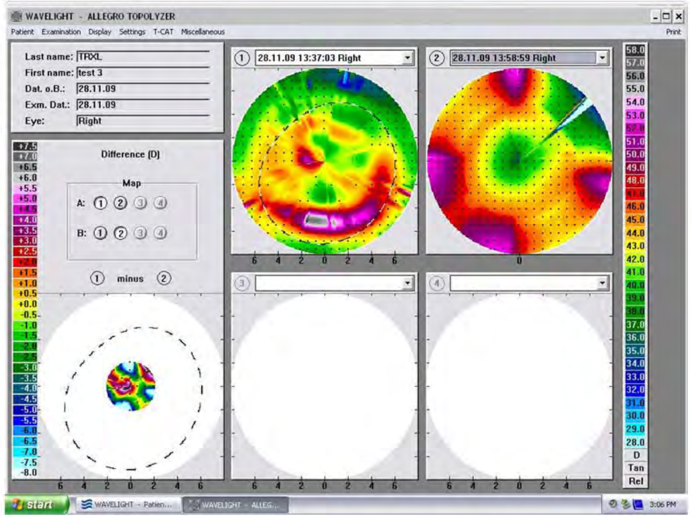
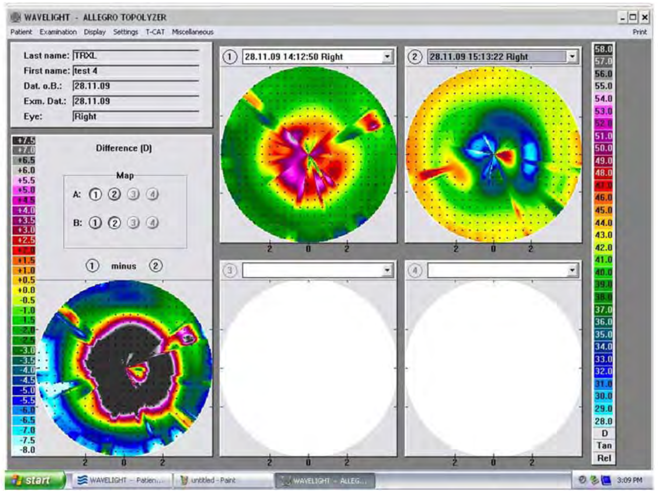
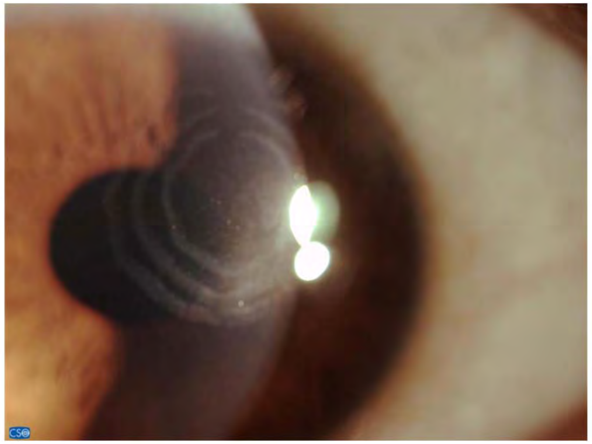
Pre-post Central flattening

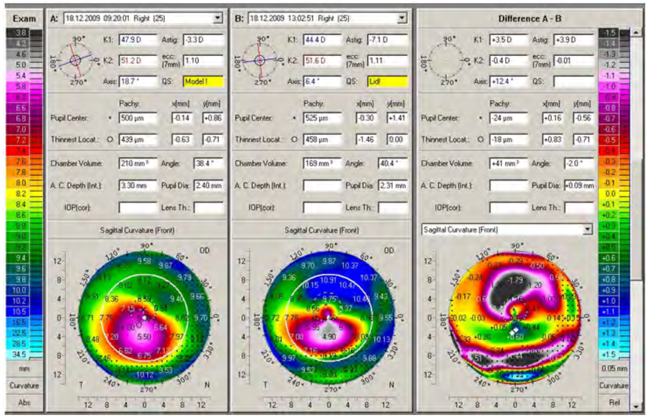




10 minutes postop, First clinical case

8 months follow-up, above case





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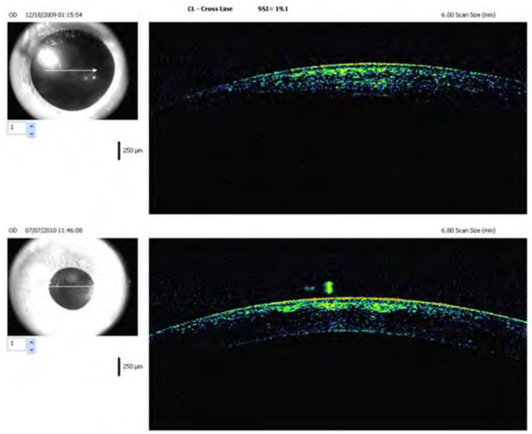
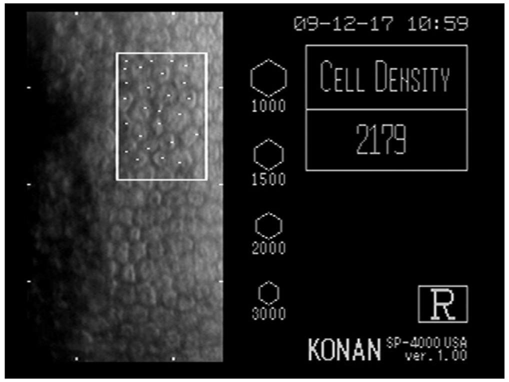
OCT and ECC images of the first clinical case pre-post

Results: The laser treatment was noted by mid-stroma whitening, but no epithelial defect. Both topography measurements documented significant uniform cornea flattening of 4-8 diopters in a central round zone of 5 mm. cOCT documented stroma hypereflectivity 50 to 350 microns depth.

Conclusions: This novel, minimally invasive laser and CXL technique may provide an alternative for myopic cornea correction without tissue removal. Further studies are required to validate the efficacy and long term stability of these findings.





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Discussion

- Thermal corrections for myopia and hyperopia have been reported earlier. Our earlier experiments have demonstrated(un-published) the criticality of epithelial & Bowman's layer preservation for effective crosslinking post-thermally. We also hypothesize that the quality of vision outcome is related to the quality of lesion placement and degree of opacity within the 3-dimensional stromal collagen matrix. We have observed that shrinkage from thermal lesions at programmable diameter/depth can be titrated to control corneal surface shape changes that can then be made durable following crosslinking. Deeper sub-surface lesions tend to make the cornea steeper while superficially placed rings make cornea flatter when rings of the same diameter are embedded mid-stromally. Furthermore, numbers of rings and diameters have a direct (linear) refractive effect for the same power/speed combination. This epi-sparing reshaping then stabilizing technique is clearly a minimally invasive novel approach in refractive manipulation of the cornea. Our small clinical study showed a significant refractive change immediate post delivery that was consistent in all the cases performed (i.e. did not induce significant astigmatism or HOAs).
- Some of the interesting findings were that the laser application did not affect the corneal epithelium or in most cases, even the Bowman's membrane at all. There was no abrasion or thermal effect on the corneal epithelium and thus is likely to preserve the nerve plexus. The laser application appeared to cause collagen shrinkage that could be constrained ("endothelium-sparing") as needed to approximately 50% depth of the cornea. This was confirmed on SLA/Topo evaluation of these corneas after the procedure as well as the corneal OCTs performed.
- We also employed transepithelial collagen cross-linking in order to maintain an intact epithelium which is the unique concept in this procedure. In order to achieve that we utilized benzalkonium chloride, 0.1% Riboflavin sodium phosphate drops. The purpose of these drops was to loosen the hemidesmosome links between the cornea epithelial cells and allow the large molecule of Riboflavin to sink into the corneal stroma and achieve collagen cross -linking.   Cross-linking efficiencies (ROS lifetimes) were enhanced with D2O as well.

Discussion 2

- The purpose of sequencing collagen cross-linking in the thermal (TS-RXL) procedure is to enhance persistence of the collagen shrinkage effect of the continuous wave laser application. This procedure offers several advantages. One is the ability to titrate the amount of refractive change (+/-) applied in the cornea via number and diameter of thermal rings applied/selected. Another advantage is that the delivery can be "free form", i.e. these rings can be moved on the applanated surface of the cornea, to potentially be (de)centered over any ectatic part of the cornea and respectively shrink that part of the cornea and flatten the ectasia. "Bowtie" patterns for astigmatic corrections, reported elsewhere, are easily programmable. A large part of the thermal outcome unpredictability is reportedly due to the variability in lesion characteristics (estimated to be >30% reported by one group): volumetric size, shape, depth below epithelium, length, rate of formation AND degree of opacity (denaturation) matter. The "Thermal Rembrandt" device presented in this report provides for significant intra-operative lesional control over prior efforts in this area. The fast precisision scanner has fine positional and time/temperature control for thermal energy deposition over the entire corneo-scleral tissue. The chilled applanation lens/laser scanner combination can control the depth of lesion formation. Additionally, an online OCT device for direct thermal laser modulation during delivery is being developed in an upcoming prototype.
- TS-RXL appears to be able to both flatten and steepen the cornea, and elasto-modulate the sclera depending on the diameter and depth of laser application (shrinkage) and being coupled with transepithelial collagen cross-linking provides a novel no cut, no implant, no stitch, no glue, no pain procedure with no epithelium defect, therefore very little discomfort post-operatively and very low risk for exposure of the cornea to infectious complications.
- Further clinical studies are needed to validate these findings into clinical practice and potentially make this novel procedure a practical alternative to the long term correction of myopia, hyperopia, astigmatism, presbyopia and potentially ectasia as well.