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Cornea "Shrinking" Techniques

Conductive Keratoplasty, Laser Thermal Keratoplasty, and Intrastromal Femtosecond Laser-Based Procedures

Tatiana L. Naoumidi, MD, PhD and Ioannis G. Pallikaris, MD, PhD

In this chapter, we will discuss why, how, and at what cost cornea "shrinking" techniques, such as conductive keratoplasty (CK), laser thermal keratoplasty (LTK with Holmium:YAG laser), and the newest, intrastromal femtosecond laser-based procedure (INTRACOR), can be applied to treat presbyopia.

Cornea shrinking techniques are usually considered to be more friendly to the cornea than photoablative procedures because, with these techniques, the central clear optical zone of the cornea remains intact, the corneal tissue is generally not removed, flap complications are absent, and no implants are inserted into the cornea.

The whole concept of these techniques dates back to more than 100 years ago, when Lans[1] demonstrated that localized heating of the cornea could change its curvature by inducing collagen shrinkage. Gasset and Kaufman[2] first performed thermokeratoplasty as a possible surgical method for flattening keratoconus via central contraction of stromal collagen in 1975. This, unfortunately, resulted in delayed epithelial healing, corneal scars, recurrent erosions, and corneal neovascularization.[2] A few years later, Aquavella et al[3] reported that this type of thermokeratoplasty caused stromal melting and perforation due to dissolution of stromal collagen at high temperatures in some patients. Thermal damage to basement membrane, as well as frequent destruction of Bowman layer during treatment, resulted in persistent epithelial defects, recurrent erosions, and superficial stromal scarring.[3] A new modification, Los Alamos thermokeratoplasty, involved heating deep stromal collagen without raising the temperature of the epithelium or Bowman's layer to destructive levels, but again, this procedure was not able to provide a lasting effect.

In 1981, Fyodorov came close to today's concept of thermokeratoplasty by developing a technique that used a hot nickel-chromium probe preset to penetrate the cornea to 95% of its depth. The technique produced thermal burns in the periphery of the cornea in the attempt to change its curvature by flattening the peripheral and steepening the central cornea.[4] The same procedure of radial thermal keratoplasty (Fyodorov's technique) was performed by Portelinha et al[4] and resulted in total regression in 12 of 16 hyperopic eyes. Low efficacy, predictability, and high complication rates were the downside of the procedure. The results had to be enhanced by laser in situ keratomileusis (LASIK).[4] Peyman et al[5] also attempted to correct a positive spherical error with

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a carbon dioxide laser. Unfortunately, the procedure resulted in superficial retraction of corneal collagen and early regression of the refractive effect.

Poor refractive outcome, along with the high complication rate, of the first thermokeratoplasty techniques gave rise to the development of other laser and radio-frequency thermal keratoplasty procedures—laser thermal keratoplasty[6-11] and, later, conductive keratoplasty.[12-17]

A technique of contact thermal keratoplasty with the use of Holmium:YAG laser, LTK for the treatment of hyperopia up to +5.00 D was introduced in 1990 by Seiler et al.[10] A few years later, noncontact LTK techniques[6-9,11] gained more ground than the previous variations.

In 1993, Mendez and Mendez[12] began to work on CK, the procedure involving high-frequency current brought into contact with the collagen fibers of the stroma with a keratoplast tip, which was inserted into the cornea to the depth of 500 μm. The procedure was performed in the periphery of the cornea in the optical zones of 6-, 7-, and 8-mm diameters.[12]

Much later, in October 2007, the Colombian eye surgeon, Luis Ruiz, performed the first INTRACOR procedure to correct presbyopia in plano emmetropes.[18] The technique utilizes a femtosecond laser to create a series of concentric rings in the stroma of the cornea underneath the epithelium. Outside the central clear zone, the cornea reportedly alters its shape to expand depth of focus (DOF).[18]

Principles of Action

When attempting to shrink corneal collagen through heating, the temperature gap is very important. Temperatures of less than 30°C to 50°C[19] minimally affect the biochemical properties of the cornea. When heated to 55°C to 58°C, human corneal collagen shrinks to one-third of its length (30% to 50%). This leads to local flattening of the corneal surface. At higher temperatures, heat-sensitive intermolecular bonds between collagen fibers begin to dissolve, resulting in corneal necrosis, scarring, and permanent destruction of corneal tissue.[19]

The basic difference between the laser- and radio frequency-based treatments lies in the mechanism of their action.

The idea of noncontact LTK with a Holmium:YAG laser was to apply a simultaneous circular pattern of 8 spots per 800 μm in diameter to the periphery of the cornea to produce collagen shrinkage and change the corneal shape to a more prolate center. The energy produced was divided into 10 pulses, elevating the stromal temperature. Up to 3 circles of treatment could be applied to treat hyperopia or to induce monovision and treat presbyopia. The procedure was mostly applied for the treatment of hyperopia.

With LTK, the thermal energy applied by the Holmium:YAG laser to the surface of the cornea is absorbed not only by the tears on the surface of the cornea but also by the surrounding tissue differentially along a thermal gradient through the depth of the treatment site (the anterior cornea developing a higher temperature). In addition, leukomas at the treatment site may function as filters during the thermokeratoplasty procedure.[20] The above characteristics are confirmed by the histological findings in LTK-treated corneas reported mostly in animal studies; the maximum volume of tissue alterations is observed in the upper corneal layers (epithelium, Bowman's, and superficial stroma), fading out toward the deeper parts of the cornea. The area of collagen alterations has a conical shape.[8,10] Morphological changes induced by LTK cause regression of the effect produced by holmium laser, as reported by Ayala et al.[8] These changes include intense tissue damage associated with an inflammatory reaction, prior to the formation of new collagen tissue of the cornea. Koch et al[11] demonstrated acute epithelial and stromal tissue changes following an LTK treatment, which, in rabbit corneas, stimulated a brisk wound healing response. According to those authors, the changes could contribute to postoperative regression of induced refractive correction LTK treatment.[11]

With CK, the tissue temperature elevation is induced by electric impedance in the flow of energy through corneal tissue, causing collagen shrinkage when the temperature reaches 65°C. Conductive keratoplasty utilizes the electrical conductive properties of the corneal tissue to propagate energy through the stroma.[20] Tissue resistance to current flow generates localized heat, whereas the delivery probe, inserted approximately to 80% of the cornea's depth (500 μm), remains cool. The thermal effect proceeds from the bottom up as it finds the path of least resistance. As a result, CK-treated tissue is exposed to the same temperature at the tip of the probe deep in the stroma as at the top of the probe on the corneal surface.[20] According to a thermal model, the treatment zone reaches the temperature of 65°C to 75°C, producing a cylindrical footprint.

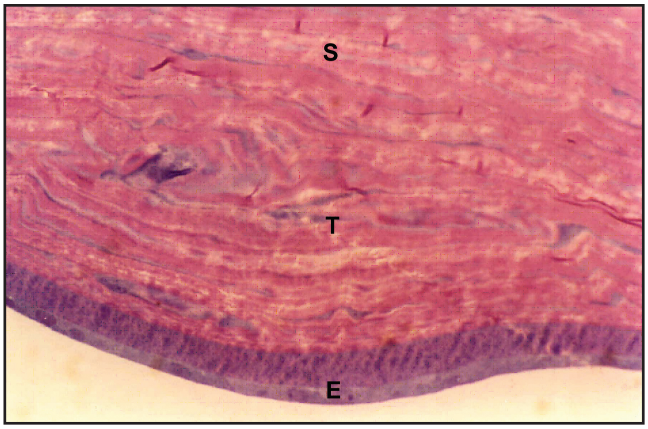

Figure 24-1. Crumpled collagen layers in the area of a conductive keratoplasty spot 3 days after treatment (human cornea). Note the depth of the corneal alterations and the integrity of the endothelium and Descemet membrane. Light microscopy, original magnification x200. S, stroma; T, border of the CK treated area; E, endothelium.

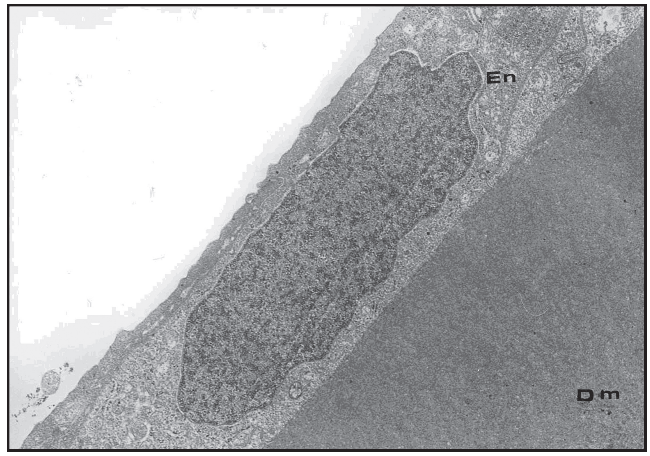

Figure 24-2. Posterior stroma, Descemet membrane, and endothelial layer immediately beneath the central part of the CK treatment zone 24 hours after CK treatment (human cornea). Note the continuous endothelial layer and the absence of endothelial edema or detachment from Descemet membrane. Electron microscopy, original magnification x5000. En, endothelium; Dm, Descemet's membrane.

According to a post-CK histological study of human corneas,[15] the treatment-induced "crumpling" changes of collagen fibers observed up to the end of the 6-month follow-up period. On day 1 postoperatively, the total thickness of the Bowman layer remained unaltered. The epithelium appeared slightly disrupted, most probably due to trauma caused by the tip's penetration. The cells, however, were viable. No signs of cell fragmentation or loss of intercellular contacts were observed. A moderate enlargement of the intercellular spaces in the area, an indicator of slight edema, was also present. By the third postoperative day, the integrity of the epithelial layer was restored. The cylindrically shaped areas reached the depth of approximately 500 µm, corresponding to 75% to 80% of the stromal thickness at the 6-mm optical zone (Figure 24-1). According to the study, no alterations of endothelium or Descemet membrane were observed at the end of 6 months' follow-up (Figure 24-2).[15] The depth and shape of the alteration site, absence of inflammatory cells or severe necrosis, along with minor epithelial damage are thought to contribute to the stability of the achieved effect.[15]

The CK procedure uses a probe, which is inserted into the cornea in a spot-by-spot manner, completing circles of 8 spots starting at the 7-mm optical zone and expanding, if demanded by the nomogram, to the 8- and (rarely) 6-mm premarked optical zones (Figure 24-3).

The circle of collagen shrinkage in the periphery results in steepening of the central cornea (Figure 24-4) and correction of presbyopia and/or hyperopia

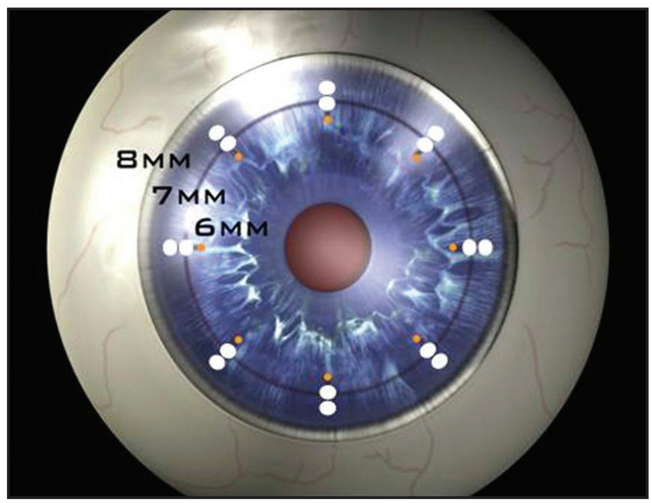

Figure 24-3. Conductive keratoplasty template with 2 circles of spots applied at the 7- and 8-mm optical zones, which is a common presbyopia treatment pattern.

(both applications are US Food and Drug Administration [FDA]-approved). When treating a plano presbyope, CK spots will be applied in the nondominant eye. The total procedure time is 1 to 2 minutes. Adding extra spots to the flat meridian of astigmatism (minus cylinder axis) enables a surgeon to treat an astigmatic component as well as to perform a series of customized operations, such as cases of previously decentered ablation, corneal trauma, or even keratoconus.[13]

A new procedure that could also be defined as a cornea shrinking technique is the femtosecond

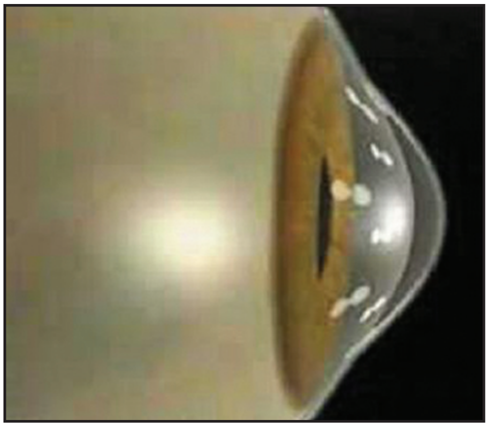

Figure 24-4. Conductive keratoplasty-induced prolate shape of the central cornea (sketch).

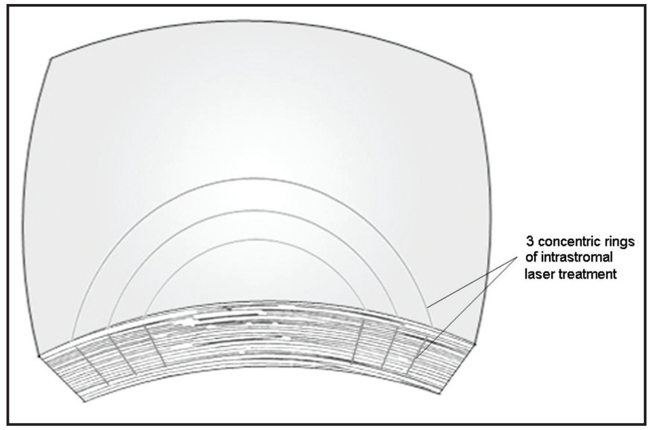

Figure 24-5. INTRACOR concentric circles in the stroma of the cornea underneath the epithelium.

laser-based intrastromal procedure—INTRACOR. This technique, introduced by Ruiz in 2007, is applied to a nondominant eye to treat presbyopia.[18] It uses a focused beam to create plasma in corneal tissue. The plasma expands and creates a bubble that then collapses, creating a space. Multiple miniscule bubbles are created within the corneal layers. These allow the entire tissue layer directly above the bubbles to collapse onto the layer below. In this way, a whole section of tissue is accurately removed, which changes the overall corneal shape and, therefore, power in a predetermined way (Figure 24-5).[18,21]

These laser-produced internal concentric rings steepen the curvature of a small central zone in the cornea, giving the eye added optical power for near tasks. Outside the central near zone, the cornea is believed to gradually change its shape to introduce negative spherical aberration and expand DOF for computer work and other tasks at arm's length. The cornea outside the largest ring produced by the laser maintains the proper shape for clear distance vision. The epithelium above the treated areas is left untouched.[18,21] Other advantages are similar to those techniques discussed previously—quick procedure time (approximately 20 seconds), no LASIK flaps, small amount of tissue removed, and a small potential for inflammatory complications. Unfortunately, the described theory is still to be confirmed by long-term studies and histology reports of this new technique.

Patient Selection

The best candidates for a cornea shrinking procedure are presbyopic emmetropes (otherwise called plano presbyopes) older than 45 years of age with significant presbyopic symptoms. It is important to note that, with CL or LTK, it is possible to treat low hyperopia[6,7,14] or even hyperopic astigmatism,[13] along with presbyopia.[16,17] The cornea shrinking procedures can be performed on either 1 or 2 eyes of the patient. In patients where CK is used to treat presbyopic symptoms in a presbyopic emmetrope, it is performed only on the nondominant eye.[16,17] Accurate determination of eye dominance is essential in these patients. A surgeon can use a sighting dominance test, such as the alternate occlusion test, camera-to-the-eye method, or a simple hole-in-the-hand method, for assessing eye dominance. It is also advised to use a "loose lens" test[17] or a preoperative monovision contact lens trial to assess tolerance for this type of correction. Usually, an amount of +1.25 D near vision correction is induced in the nondominant eye. Either way, a wrong dominance assessment and, as a result, treatment of presbyopic symptoms in a dominant eye with CK would lead to patient dissatisfaction. When treating with INTRACOR for presbyopia, some surgeons opt for a nondominant eye treatment,[18] whereas others also treat patients bilaterally[21] depending on the individual's special needs. This technique is relatively new, and the protocols are yet to be standardized.

No matter which of the discussed techniques is applied, patients suffering from existing or chronic ocular or systemic diseases, a history of ocular surgery or trauma, steroid-responsive increase in intraocular pressure, or unstable, progressive hyperopia or myopia are not the best candidates for this type of treatment. Contact lens users are advised to discontinue their lens use 21 to 30 days prior to the procedure. To proceed with a cornea shrinking procedure, a surgeon must be sure the patient has a clear corneal image in slit-lamp microscope examination, undistorted mires in the central keratometry examination, and ultrasound pachymetry readings of at least 550 μm at the 6-mm zone so that damage to Descemet membrane or the endothelium of the treated corneas can be avoided.

RESULTS

Within the 1-year FDA clinical trial, 143 eyes of 143 presbyopic patients were treated with CK in the nondominant eye.[17] For near vision correction, the target refraction was up to -2.00 D in the nondominant eye, and was 0.0 D for distance vision correction. Enrolled patients had a preoperative spherical equivalent of plano to +2.00 D, no more than 0.75 D refractive astigmatism, and were aged 40 years or older. At 6 months postoperatively, 77% had uncorrected near vision of J3 or better. A total of 85% of all patients had binocular uncorrected distance visual acuity (UCVA) of 20/25 or better along with J3 or better near. Sixty-six percent of eyes treated for near had a manifest refractive spherical equivalent (MRSE) within ±0.50 D of the intended value at 6 months. In 89% of eyes, the MRSE changed 0.05 D or less between 3 and 6 months postoperatively.[17] These results agree with the previously conducted CK studies.[14,16]

It is difficult to discuss LTK results in this chapter, as the procedure has mostly been applied for the treatment of hyperopia. The majority of surgeons performing LTK agreed on the low predictability of the technique.[6-8,11] Nano and Muzzin[7] reported 46% of eyes to be within ±1.00 D of plano. Twelve months after surgery, the initial spherical equivalent refraction was reduced only by half (+2.50 ±0.87 D was reduced to +1.25 ±0.96 D). Alio et al[6] reported that 57.8% of the treated eyes were within ±1.00 D of intended refraction. However, an LTK study by Rocha et al[9] reported that the technique had high predictability and efficacy; 92% of the eyes were within ±0.50 D of plano, and 100% were within ±1.00 D. Uncorrected visual acuity was 20/40 or better in 100% of eyes and 20/20 or better in 84% at 2 years postoperatively.[9] In terms of efficacy, Alio et al[6] reported a UCVA of 20/20 or better in 47% of eyes and 20/40 or better in 72% of eyes at 15 months.

Since LTK technology was introduced, regression has been a major topic for discussion. The maximum volume of tissue alterations is observed in the epithelium, Bowman's layer, and superficial stroma, and fades out toward the deeper parts of the cornea.[8]

To date, few studies have reported on the INTRACOR procedure for the treatment of presbyopia.[18,21] Ruiz, the procedure's pioneer, reported 83 eyes of 45 presbyopic patients treated with femtosecond laser-based intrastromal procedure with the use of the Technolas laser. At 6 months postoperatively, all 83 eyes (100%) had improved uncorrected near visual acuity (UNVA), with minimal or no change in uncorrected distance visual acuity (UDVA). Twenty-two eyes were available at 12 months; UNVA improved to J1 in these eyes with continued improvement in mean UDVA. At last follow-up, a mild myopic shift in refraction was noted in 4% of the treated eyes, showing a 2- or 3-line decrease of UDVA, and 89% of the eyes achieved both J2 and 20/25 or better.[18] Another INTRACOR study, conducted by Holzer et al,[21] reported 25 eyes of 25 patients who were treated for presbyopia and followed for 3 months. The mean postoperative UNVA increased from preoperative 0.7 ±0.16 logMAR to 0.26 ±0.21 logMAR, and the mean UDVA changed slightly from 0.11 ±0.11 logMAR to 0.05 ±-0.1 logMAR at 3 months. Regarding best distance correction, mean sphere changed from +0.75 ±0.23 D preoperatively to +0.15 ±0.31 D postoperatively, and mean cylinder changed from -0.33 ±0.17 D to -0.42 ±0.23 D.[21]

COMPLICATIONS

Of the 3 discussed cornea shrinking procedures, CK remains the only one approved by the FDA for the treatment of presbyopic symptoms in emmetropic and hyperopic eyes. Within the FDA clinical study of 143 eyes, no eye had a corrected distance visual acuity worse than 20/40 or had an increase of cylinder >2.00 D.[17] No sight-threatening device or surgeon-related complications were observed either intra- or postoperatively. The most common postoperative complaints were discomfort and foreign-body sensation during the first 3 days, accompanied in some patients by light sensitivity.[13,14]

It is believed that induction of cylinder is the major safety setback of CK; increase of cylinder occurs if the cornea is not marked properly prior to surgery or in cases where spots are not applied symmetrically according to the marking. Other causes of induced cylinder were the inconsistent pressure of the CK probe on the cornea and shallow insertion of the probe into the stroma. These issues were addressed with the introduction of a corneal template that enables a surgeon to achieve repeatable depth of the tissue penetration, along with high spot symmetry.

With the INTRACOR procedure, the maintenance of the epithelium integrity definitely contributes to greater patient comfort postoperatively. Ruiz et al reported stability of pachymetry, endothelial cell density, and contrast sensitivity.[18] Vision is reported to be blurred for a short period of time (several hours) due to a formation of gas bubbles in the cornea.[18,21] A delay in the bubble dissolution could lead to disappointment for the patient postoperatively. In the early postoperative period, most patients reported seeing halos, especially at night. These complaints reportedly diminished over time.[21] Apart from these optical setbacks, femtosecond lasers are known for their high reproducibility rate and high predictability of the results. This INTRACOR technique is much less surgeon-dependent than the previously described modalities.

Summary

Stability of the achieved refractive result and reproducibility of the treatment are the most important issues with thermokeratoplasty techniques. Introduction of a CK template for better centration and reduction of induced astigmatism definitely helped. The ability to add another circle of treatment when presbyopia progresses over several years is also essential to keep this surgical option viable in the presbyopia market.

We do not believe that Ho:YAG laser techniques as we know them today have serious potential as presbyopia treatment procedures. However, it has been suggested that a newer version of LTK could possibly overcome the weaknesses of the previous generation of LTK machinery. If and when this happens, a simultaneous and quick application of a treatment circle without significant epithelium damage and probably a deeper and more homogenous penetration into the corneal stroma could become the long anticipated assets of LTK.

To date, not much can be said about the INTRACOR femtosecond procedure due to the lack of histological studies and sufficient numbers of the treated patients. Any permanent structural change made to the cornea is a definite setback of a new technique. As soon as the INTRACOR treatment protocols are standardized and the technique is FDA-approved, it has the biggest potential for further developments. This promising procedure has yet to be observed through long-term follow-up of the treated patients. It is also important to perform post-INTRACOR retreatments and to apply the procedure not only for presbyopic, but also ametropic patients.

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