Conductive Keratoplasty for the Correction of Low to Moderate Hyperopia: U.S. Clinical Trial 1-Year Results on 355 Eyes

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Objective: To document the 1-year safety, efficacy, and stability results of 355 eyes treated in the multicenter study of conductive keratoplasty (CK) used to correct low to moderate hyperopia.

Design: Nonrandomized comparative (self-controlled) trial.

Participants: Twenty surgeons at 13 centers performed CK on the eyes of all patients enrolled in a multicenter, 2-year, U.S. phase III clinical trial. Treated eyes had +0.75 to +3.00 diopters (D) of hyperopia and ≤0.75 D of cylinder. Patients were 40 years of age or older.

Intervention: Low-energy, high-frequency current was applied directly into the peripheral corneal stroma through a delivery tip inserted at 8 to 32 treatment spots. The number of treatment spots was increased for increasing levels of hyperopia, but the amount of radiofrequency energy remained constant. Emmetropia was intended. All eyes were treated once (there were no retreatments).

Main Outcome Measures: Data from 355 eyes with 1 year of follow-up were analyzed for safety and stability, and data from 318 eyes were analyzed for efficacy and predictability, as well as stability and safety. All patients reported on satisfaction and quality of vision after surgery.

Results: At 1 year, uncorrected visual acuity was ≤20/20 in 56%, ≤20/25 in 75%, and ≤20/40 in 92% of eyes. The manifest refractive spherical equivalent refraction was within 0.50 D in 63%, within ±1.00 D in 89%, and within ±2.00 D in 99%. Seven of 355 eyes lost 2 lines of best spectacle-corrected visual acuity at 1 year, but no eye lost >2 lines. One eye of 355 had induced cylinder of >2.00 D. The cycloplegic refractive spherical equivalent changed a mean of 0.25 ± 0.50 D between months 3 and 6, 0.11 ± 0.41 D between months 6 and 9, and 0.11 ± 0.35 D between months 9 and 12. Refractive stability seemed to be attained by 6 months and remained stable through 12 months. Histology and confocal microscopy showed deep penetration of the treatment into the stroma. Endothelial cell counts were not changed by the treatment.

Conclusions: CK seems to be safe, effective, and stable for correcting low to moderate spherical hyperopia in patients 40 years old or older. Treatment penetration is deep and cylindrical in shape, and it does not damage the corneal endothelium. Uncorrected visual acuity, predictability, and stability are as good as or better than those obtained with other techniques used to correct hyperopia. *Ophthalmology 2002;109:1978–1989 © 2002 by the American Academy of Ophthalmology, Inc.*

Originally received: November 11, 2001.
Accepted: April 11, 2002. Manuscript no. AA 210583

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The members of the Conductive Keratoplasty United States Investigators Group are listed in the appendix.

Presented in part at the Annual Meeting of the American Academy of Ophthalmology, New Orleans, Louisiana, November, 2001.

Drs. Hersh, Manche, Maloney, and Davidorf and the Conductive Keratoplasty Investigators Group participated as clinical investigators in this Food and Drug Administration phase III study sponsored by Refractec, Inc. (Irvine, CA). These authors participate on Refractec's Medical Advisory Board and are paid for their time. They otherwise have no proprietary or financial interest in the ViewPoint conductive keratoplasty system from Refractec, Inc. Dr. Moataz Sabry was not an investigator but provided the confocal microscopy photographs. Dr. Marguerite McDonald is a paid medical monitor for the phase III study on conductive keratoplasty by Refractec, Inc.

The nature of the procedure was explained to all participating patients, and they all signed informed consent forms before undergoing the procedure.

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Development of thermal techniques to shrink peripheral corneal collagen and thereby steepen the central cornea has challenged ophthalmologists for longer than 100 years. Hot-wire thermokeratoplasty, used in the 1980s to produce thermal burns that penetrated to 95% of corneal depth in hyperopic eyes, showed a lack of predictability and stability, and further development was abandoned.[1–4] More current

ISSN 0161-6420/02/$–see front matter
PII S0161-6420(02)01255-1

Table 1. Original and Current Nomograms

Number of Treatment Spots	Original Nomogram	Current Nomogram
8*	+0.75 D to < + 1.00 D	+0.75 D to +0.875 D
16	+1.00 D to < + 2.00 D	+1.0 D to +1.625 D
24	+2.00 D to < + 3.00 D	+1.75 D to +2.25 D
32	+3.00 D to < + 4.00 D	+2.375 D to +3.00 D

* None of the first 54 eyes were treated with 8 spots.
D = diopters.

techniques using thermal keratoplasty include noncontact holmium:yttrium–aluminum–garnet laser thermal keratoplasty (Ho:YAG)(LTK; Sunrise Technologies, Fremont, CA),[5–9] contact holmium:yttrium–aluminum–garnet LTK (Holmium 25; Technomed, Baesweiler, Germany),[9–12] continuous-wave diode LTK (DTK; Rodenstock, ProLaser Medical Systems, Inc., Dusseldorf, Germany),[13,14] and conductive keratoplasty (CK; ViewPoint; Refractec, Inc., Irvine, CA).[15] Nonthermal, excimer laser–based techniques for correcting hyperopia include photorefractive keratectomy[16–21] and laser in situ keratomileusis.[22–28]

CK is a laserless radiofrequency-based technique for the correction of low to moderate hyperopia. The treatment produces a homogenous temperature increase that shrinks collagen in the treated area and forms a cylindrical footprint deep in the stroma. After a full circle of treatment spots, the peripheral cornea flattens and the central corneal steepens. This article presents the 1-year, single-treatment results of 355 available eyes of the 401 enrolled in a U.S. phase III Food and Drug Administration (FDA) clinical trial and compares them with results obtained with other nonexcimer laser techniques for the correction of hyperopia.

Materials and Methods

Study Design

This is a report of the 12-month results from the cohort of consecutive enrolled patients whose eyes were treated in a prospective, consecutive-series, multicenter clinical study (FDA phase III) evaluating the safety, efficacy, and stability of the CK procedure for the correction of 0.75 to 3.00 diopters (D) of hyperopia and ≤0.75 D of cylinder. The study follow-up will be 24 months.

One-year data are available from 318 eyes for the variables that indicate treatment efficacy (uncorrected visual acuity [UCVA], best spectacle-corrected visual acuity [BSCVA], manifest refractive spherical equivalent refraction [MRSE], and cycloplegic refractive spherical equivalent). For variables that indicate treatment safety and stability, data are available for 355 eyes. The discrepancy in number of eyes can be accounted for by the change in nomogram after treatment of the first 54 eyes. The original nomogram specifying the number of treatment spots to correct a given level of hyperopia was modified after the first 54 eyes were treated because it had a tendency toward undercorrection (Table 1). Data from 24 of those 54 eyes could not be analyzed for efficacy variables but could be analyzed for safety and stability. The remaining 30 eyes, however, were found to have been treated with the number of spots indicated by what later became the revised (current) nomogram and were included in efficacy analyses. For example, an eye with 1.50 D of hyperopia would be treated with 16 spots under both the original and current nomograms, and the efficacy results could be included in the current nomogram eyes.

Figure 1. The ViewPoint conductive keratoplasty system, including the handpiece with the Keratoplast tip and a choice of two lid specula that act as the electrical return path. The console weighs 14 pounds.

Study Device

The ViewPoint CK system (Fig 1) used to perform the CK procedure consists of a radiofrequency energy-generating console; a handheld, reusable, pen-shaped handpiece attached by a removable cable and connector; a foot pedal that controls the release of radiofrequency energy; and a speculum that provides a large surface for an electrical return path. The energy level default is 60% of 1 W, and the exposure time default is 0.6 seconds. Attached to the probe is a single-use, disposable, stainless-steel Keratoplast Refractec Inc., Irvine, California tip, 90 μm in diameter and 450 μm long, that delivers the current directly to the corneal stroma (Fig 2). The tip has a proximal bend of 45° and a distal bend of 90° to allow access to the cornea over the patient's brow and nasal regions. At the very distal portion of the tip is an insulated stainless-steel stop (cuff) that ensures correct depth of penetration.

Figure 2. Conductive keratoplasty handpiece with Keratoplast tip (90 μm wide, 450 μm long) and insulated stop at the distal end. Shown next to a 7-0 suture.

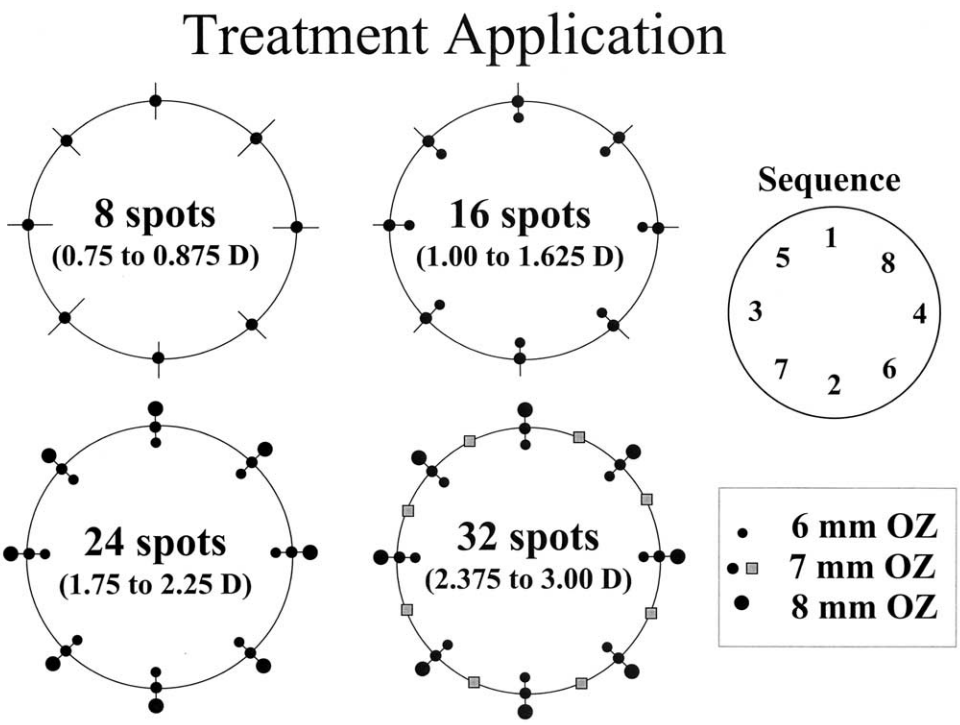


Figure 3. Treatment application. D = diopter; OZ = optical zone.

Patients

Institutional review board approval was obtained at each institution. A total of 401 patients at 13 centers in the United States who met eligibility requirements were enrolled consecutively into the study from February 10, 1999, to December 1, 2000, signed informed consent forms, and had 8 to 32 treatment spots applied to the cornea during the CK procedure. The intended correction was emmetropia.

Enrolled patients had no existing ocular or chronic systemic disease, previous ocular surgery, history of herpes infection, steroid-responsive increase in intraocular pressure, intractable keratoconjunctivitis sicca, history of keloid formation, or unstable, progressive hyperopia. Hard contact lens wearers were to discontinue lens use 3 weeks before the final measurements and the procedure, and soft contact lens wearers were to discontinue lens use 2 weeks before the final measurements and the procedure. They also had to have clear, undistorted mires on the central keratometry examination. Eyes with pachymetry readings of <560 μm at the 6-mm optical zone (OZ) and those with a distance UCVA of better than 20/32 were excluded from study participation.

Examination Methods

The preoperative and postoperative examinations for all eyes included manifest and cycloplegic refractions; uncorrected visual acuity and BSCVA with use of Early Treatment Diabetic Retinopathy Study visual acuity charts or Bailey–Lovie charts (distance) and Jaeger visual acuity charts (near); slit-lamp and funduscopic examination; and computerized corneal topography. Cycloplegic refraction was measured 30 minutes after two applications of one or two drops of 1% cyclopentolate 5 minutes apart. Intraocular pressure was measured with the surgeon's choice of standard applanation instruments, including Goldmann, Perkins, or Draeger tonometry.

The preoperative examinations were performed by the surgeons or their assistants 1 to 60 days before the CK procedure. Postoperative examinations were performed on days 1 and 7 and months

Table 2. Study Patient Accountability

	Month 1		Month 3		Month 6		Month 12	
	Number	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
Available for safety analysis	390/401	97%	394/401	98%	389/401	97%	355/401	89%
Available for efficacy analysis	354/363	98%	358/363	99%	352/363	97%	318/363	88%
Discontinued	1/401	0.25%	1/401	0.25%	1/401	0.25%	1/401	0.25%
Missed visit	10/401	2%	6/401	1%	11/401	3%	1/401	0.25%
Not yet eligible for interval	0/401	0%	0/401	0%	0/401	0%	40/401	10%
Lost to follow-up	0/401	0%	0/401	0%	0/401	0%	4/401	1%

Table 3. Demographic and Baseline Information

Number of Patients/Eyes	233/401
Mean age (SD)	55.3 years (6.4)
Range	40 to 74
Median	55.6
Range of Treatment CRSE	
Mean (SD)	+1.86 D (0.63)
Range	+0.75 D to +4.00 D
Median	+1.75 D
Range of Treatment MRSE	
Mean (SD)	+1.80 D (0.64)
Range	+0.38 D* to +3.75 D
Median	+1.75 D

CRSE – Cycloplegic refractive spherical equivalent; MRSE – Manifest refractive spherical equivalent.

* Includes 2 ineligible eyes with minus CRSE values.

SD = standard deviation.

1, 3, 6, 9, and 12, and results were recorded on standardized data forms. Patients were also asked to subjectively evaluate the quality of their postoperative vision and indicate their level of satisfaction on standardized forms.

Mesopic contrast sensitivity testing was performed with the Optec 1600X, both with and without a glare source, in a subset of 158 study patients before surgery and at 6 and 12 months after surgery. Testing without glare was performed with the target illumination set to 5 cd/m^2 and the glare source turned off. A trial frame with the patient's best correction and test slide 1 was inserted. The patient was asked to make a forced response to the direction (left or right) of the point of the line in boxes A1 through A8. The box number (i.e., A6) of the last correct response was recorded. This was repeated with test slide 2. The procedure was repeated with lines B1 through B8, C1 through C8, D1 through D8, and E1 through E8. The procedure for testing with glare was the same except that glare illumination was set to 2 lux.

Specular microscopy studies were performed to study the effect of the treatment on the corneal endothelium on 162 eyes at 5 of the 13 investigational sites. Measurements were taken with the Konan NonCon Robopachy (Konan Medical, Inc., Hyogo, Japan) at the central cornea, the 3-mm OZ, and the 6-mm OZ. Changes from preoperative levels at these sites were calculated by using paired-differences statistical testing.

Corneal haze was evaluated by slit lamp on a five-level scale of clear, minimal, trace, mild, moderate, and marked. The protocol failed to specify that haze only in the central cornea was to be reported and that haze at the treatment site was expected.

Confocal microscopy, a noninvasive technique for revealing histology, was performed 12 months after the procedure by using the Nidek Confoscan II (Nidek Ltd., Gamagori, Japan). This technique optically sections living tissues to allow in vivo examination of individual layers.

Surgical Procedure

Topical anesthesia was induced with one drop of 0.5% tetracaine, administered three times at 5-minute intervals. Pilocarpine was not administered. A lid speculum was placed in the eye to be treated to obtain maximal exposure and to provide the electrical return path; the fellow eye was taped closed. Illumination was provided by the operating microscope. While the patient fixated on the microscope's light, the cornea was marked with a gentian violet–dampened, eight-intersection CK marker that marks the 7-mm OZ and makes radial marks that extend from the 6-mm to the 8-mm OZs (Fig 3). The surface of the cornea was dried with a fiber-free sponge to avoid dissipation of applied energy through a damp surface. The surgeons placed the Keratoplast tip on the cornea at the treatment markings and attempted to place it perpendicular to the corneal surface. The cuff around the probe, which settles perpendicular to the cornea, helped to achieve perpendicular placement. Light pressure was applied until the tip penetrated the stroma to its insulator stop. Energy was applied by depressing the foot pedal. All eyes were treated at the default setting of 350 kHz at 60% power for 0.6 seconds.

All eyes were treated with the number of spots indicated by the current nomogram (Table 1; Fig 3). For example, for the lowest amount of correction, +0.75 to +0.875 D, eight spots were placed on the 7-mm OZ. For correcting +1.00 to +1.625 D, 16 spots were placed: 8 on the 6-mm OZ and another 8 on the 7-mm OZ. For correcting +1.75 to + 2.25 D, 24 spots were placed: 8 each on the 6-, 7-, and 8-mm OZs. For correcting +2.375 to +3.00 D, 24 spots were

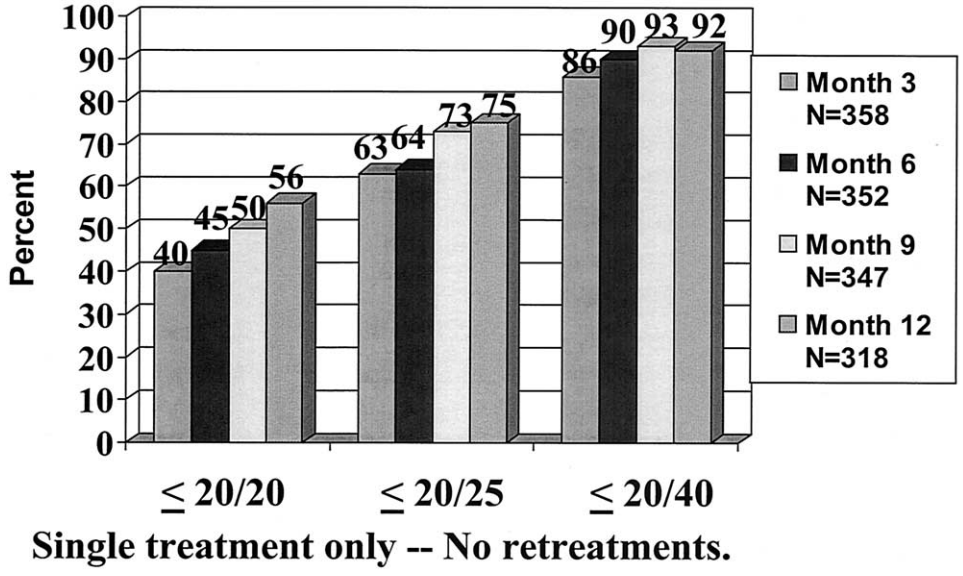


Figure 4. Postoperative uncorrected visual acuity (UCVA) over time.

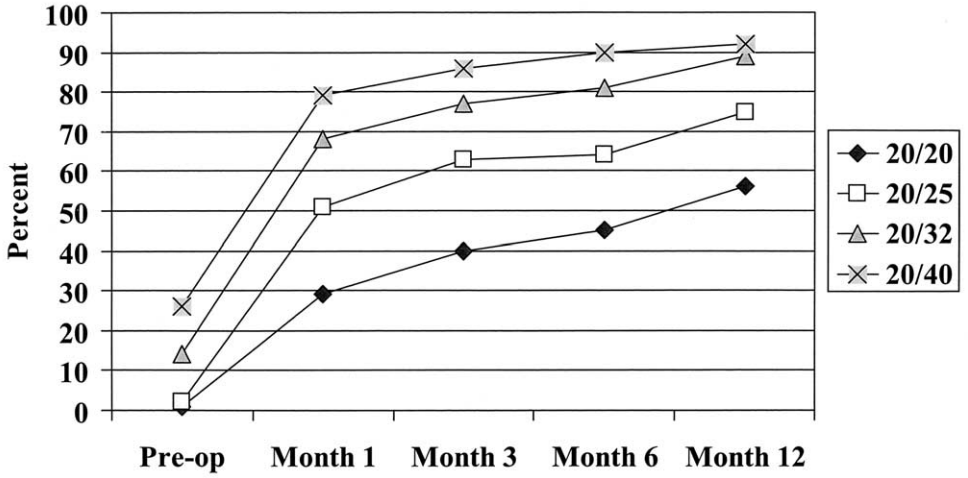


Figure 5. Change over time in uncorrected visual acuity (UCVA).

placed: 8 each were placed on the 6-, 7-, and 8-mm OZs, as were placed for +1.75 to +2.25 D of correction, and then 8 additional spots were added between the spots previously made on the 7-mm OZ. The sequence of spot placement is shown in Fig 3. The probe tip was cleaned of tissue debris with a fiber-free sponge after each treatment spot. All eyes received a single CK treatment; i.e., no retreatments were performed.

Postoperative Care

After treatment, one drop of topical antibiotic solution and one drop of diclofenac sodium 0.1% (Voltaren; Ciba Vision Ophthalmics, Duluth, Georgia) were administered and continued for 2 days. Unpreserved artificial tear solution was the only ocular medication permitted in the study. The treated eye was not patched.

Results

Accountability and Demographics

One eye was enrolled and treated, but no energy was delivered during the procedure. Thus the total number of treated eyes was 400 of the 401 enrolled (Table 2). Complete follow-up data were available for 355 eyes for safety variables and for 318 eyes for efficacy variables. The mean age of enrolled patients was 55 ± 6.4 years (range, 40–74 years). There were 136 female patients and 97 male patients. Most (81%) of the patients were white and the others were Black, Asian, or other, or the race was not recorded. Demographic information is shown in Table 3.

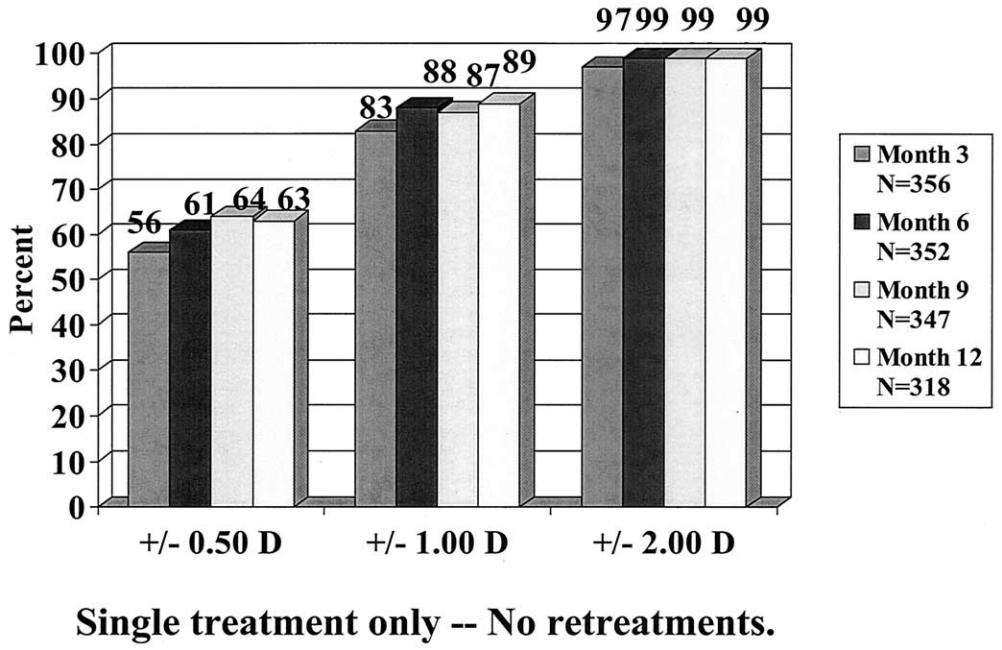
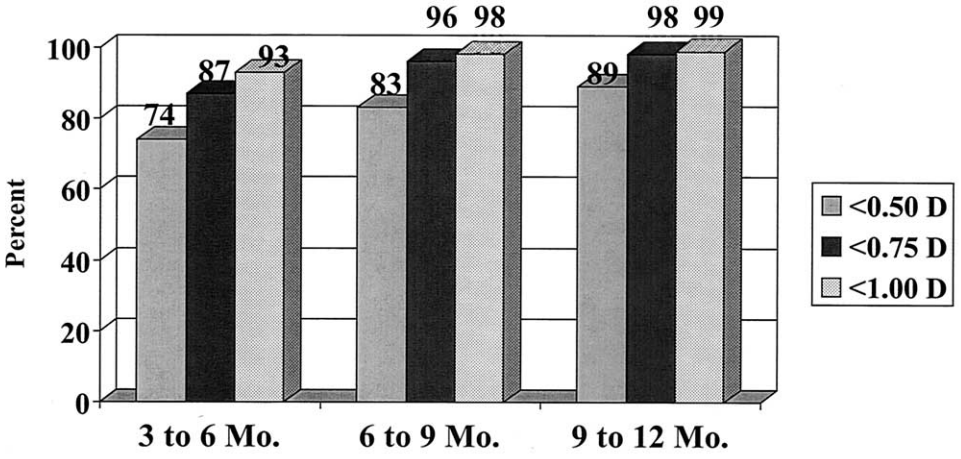


Figure 6. Predictability of achieved manifest refractive spherical equivalent (MRSE) refraction. D = diopter.



Mean Change in CRSE	0.25 D (0.50)	0.11 D (0.41)	0.11 D (0.35)
Conf. Interval	0.19, 0.31	0.07, 0.15	0.07, 0.15

Figure 7. Cycloplegic refractive spherical equivalent (CRSE) stability. All visits through 12 months. D = diopter.

Uncorrected Visual Acuity

Before treatment, 5 (1%) of 363 eyes had 20/20 or better UCVA, 96 (26%) of 363 had UCVA of 20/40 or better, and 358 (99%) of 363 had 20/200 or better. After surgery, at 1 year, 178 (56%) of 318 eyes had UCVA of 20/20 or better, 240 (75%) of 318 had 20/25 or better, 294 (92%) of 318 had 20/40 or better, 315 (97%) of 318 had 20/80 or better, and 100% had 20/200 or better. Fig 4 shows postoperative UCVA over time. Fig 5 shows UCVA changes over time for each acuity level. UCVA progressively improved with time for acuity levels of 20/20 or better, 20/25 or better, and 20/32 or better and showed no leveling off. For lower acuity levels, however, a leveling-off was apparent within the 12 months. The 20/40 acuity leveled off at 6 months, and 20/80 leveled off at approximately 1 month.

Predictability and Stability

Predictability. At 1 year, 199 (63%) of 318 eyes were within ±0.50 D of emmetropia, 282 (89%) of 318 were within ±1.00 D, and 316 (99%) of 318 were within ±2.00 D (Fig 6).

Stability. All eyes (including the early nomogram eyes) were evaluated for stability. The cycloplegic refractive spherical equivalent refraction changed ≤0.50 D in 240 (74%) of 326 eyes between the 3- and 6-month visits, in 305 (83%) of 366 between the 6- and 9-month visits, and in 301 (89%) of 340 between the 9- and 12-month visits (Fig 7). The MRSE increased a mean of 0.25 ± 0.50 D between 3 and 6 months, 0.11 ± 0.41 D between 6 and 9 months, and 0.11 ± 0.35 D between 9 and 12 months. The refraction seemed to stabilize at 6 months.

The plot of the mean MRSE (Fig 8) showed an overshoot of

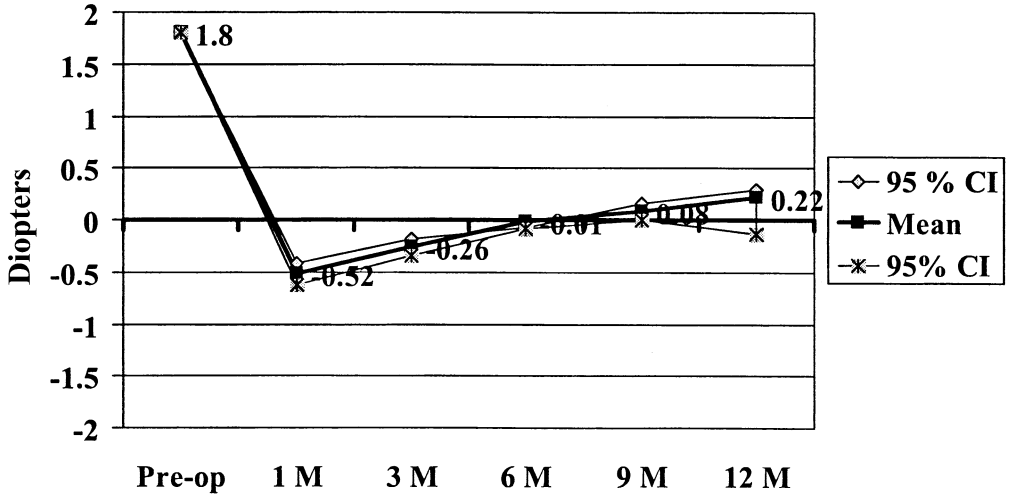


Figure 8. Mean manifest refractive spherical equivalent (MSRE) refraction (diopters) over time. Twelve-month cohort of 300 eyes treated with the current nomogram. CI = confidence interval.

Table 4. Summary Efficacy Variables

	3 Months (N = 358)	6 Months (N = 352)	12 Months (N = 344)	FDA Target
UCVA ≤20/20	40%	45%	56%	Not stipulated
UCVA ≤20/25	63%	64%	75%	Not stipulated
UCVA ≤20/40	86%	90%	92%	85%
MRSE ± 0.50 D	56%	61%	62%	50%
MRSE ± 1.00 D	83%	88%	89%	75%

MRSE = manifest refractive spherical equivalent; UCVA = uncorrected visual acuity.

approximately 0.5 D at month 1, followed by a slight regression. At 12 months, the eyes had an MRSE of 0.22 D, which is very close to emmetropia. Confidence intervals are shown surrounding the mean values (instead of standard deviations). Confidence intervals are a better indicator of deviations from mean values because they take sample size into account. Results at 6 and 12 months met all FDA guidelines for UCVA and accuracy of achieved MSRE (Table 4).

Safety

Best Spectacle-corrected Visual Acuity. Safety variable results are summarized in Table 5. Note that n = 355 for safety data (not 318, as for efficacy data) because safety data were acquired from the first 54 eyes (original nomogram) in addition to the current nomogram eyes. Twenty-five of the total 390 eyes lost >2 lines of BSCVA at 1 month, and 7 of 355 lost 2 lines at 12 months. Eight eyes lost more than two lines at 1 month, and none lost more than two lines at 12 months. However, the loss of two lines at 12 months left all seven eyes with very functional vision. Before surgery, all seven of these eyes had 20/10 to 20/16 BSCVA. After surgery, one had 20/16 BSCVA, three had 20/20, and three had 20/25. No eye had BSCVA worse than 20/40 at any follow-up visit. No eye that had 20/20 or better best-corrected vision before surgery had worse than 20/25 BSCVA after surgery.

Cylinder. Postoperative absolute cylinder increases are shown in Table 6. No change was defined as ±0.75 D. Percentages for all levels of cylinder were highest at the first month and then declined with time. At 12 months, 6% had 1.00 D of induced cylinder, and 4.2% had >1.00 D but <2.00 D of induced cylinder. A total of 88% had no change in cylinder at 12 months.

Table 5. Postoperative Visit

Safety Variable	1 Month	3 Months	6 Months	9 Months	12 Months
2 line loss BSCVA	25/390 (6%)	20/392 (5%)	16/389 (4%)	13/386 (3%)	7/381* (2%)
>2 line loss BSCVA	8/390 (2%)	4/392 (1%)	2/389 (0.5%)	2/386 (0.5%)	0/381 (0%)
BSCVA worse than 20/40	0/390 (0%)	0/392 (0%)	0/389 (0%)	0/386 (0%)	0/381 (0%)
Increase >2.00 D cylinder	13/390 (3%)	8/392 (2%)	3/389 (0.8%)	1/386 (0.3%)	1/381 (0.3%)
BSCVA worse than 20/25 if better than 20/20 preoperatively	14/390 (4%)	7/392 (2%)	3/389 (0.8%)	2/386 (0.5%)	0/381 (0%)

* Preoperatively, these eyes had 20/10 to 20/16 BSCVA. Postoperatively, 1/7 eyes had 20/16 BSCVA, 3/7 had 20/20, and 3/7 eyes had 20/25. Thus all eyes with 2-line losses had functional vision.

BSCVA = best spectacle-corrected visual acuity.

Table 6. Cylinder Changes

Cylinder Change	Month 1	Month 6	Month 12
Increase >2.00 D	13/390 3.3%	3/389 0.8%	1/355 0.3%
Increase 2.00 D	11/390 2.8%	5/389 1.3%	2/355 0.6%
Increase 1.25–1.99 D	57/390 14.6%	47/389 12.1%	15/355 4.2%
Increase 1.00 D	49/390 12.6%	40/389 10.3%	23/355 6.5%
Decrease 1.00 D	2/390 (0.5%)	1/389 (0.25%)	1/355 (0.3%)
No Change	258/390 (66.1%)	293/389 (75.3%)	311/355 (87.6%)

D = diopters.

Complications and Adverse Events. No intraoperative complications or adverse events occurred during any of the surgeries. There were no treatment-related adverse events, such as peripheral corneal defect, corneal edema later than 1 week after surgery, recurrent corneal erosion at 1 month or later, double or ghosting images at any time, foreign body sensation at 1 month or later, and pain at 1 month or later.

Corneal Haze. The investigational sites were expected to measure corneal haze at the central cornea only. However, the evaluator at one investigational center measured and reported haze at the CK treatment site, and the results in this section reflect all reports. No haze was seen in 98% (384/390) of the eyes at 1 month after surgery, in 96% of eyes at 3 months, in 97% at 6 months, or in 100% at 12 months. The highest level of haze was a mild level seen in 4 (1%) of 390 eyes at month 1 and in 1 (0.25%) of 394 eyes at months 3 and 6.

Intraocular Pressure. Mean intraocular pressure (IOP) in all treated eyes is shown in Table 7. There were no occurrences of an uncontrolled IOP increase of >5 mmHg above baseline. An IOP reading of >25 mmHg was measured in 2 of 389 eyes at 6 months and in 1 eye at 9 and 12 months. However, no patient was diagnosed with glaucoma.

Contrast Sensitivity. A comparison of the preoperative and 6-month postoperative mesopic contrast sensitivity values showed no differences for patches A, B, C, D, and E, both with (Table 8) and without (Table 9) glare.

Specular Microscopy. Table 10 shows the mean endothelial cell density counts over time, measured at the corneal center, the mid periphery, and the periphery. Mean endothelial cell density showed values of approximately 2700 cells per square millimeter for preoperative and postoperative measurements for the central, midperipheral, and peripheral corneal regions. No clinically or statistically significant changes appeared in the mean cell count

Table 7. Intraocular Pressure (mm Hg) Over Time

	Pre-op	Month 1	Month 3	Month 6	Month 12
Mean (SD)	14.9 (2.6)	14.0 (2.6)	14.0 (2.6)	14.1 (2.6)	14.3 (2.5)
95% CI	14.6, 15.1	13.7, 14.2	13.8, 14.3	13.9, 14.4	14.0, 14.7
Median	15.0	14.0	14.0	14.0	14.0
Range	8.0 to 25.0	7.0 to 23.0	6.0 to 24.0	6.0 to 26.0	9.0 to 30.0

CI = confidence interval; SD = standard deviation.

Table 8. Mesopic Contrast Sensitivity without Glare

	Preoperative N = 158	Month 6 N = 141	Month 12 N = 73
Patch A			
Mean (SD)	4.05 (1.51)	4.38 (1.91)	4.64 (1.76)
95% CI*	3.81, 4.29	4.07, 4.69	4.23, 5.05
Mean change (95% CI)	NA	0.40 (0.07, 0.73)	0.59 (0.16, 1.02)
Patch B			
Mean (SD)	3.74 (1.80)	4.09 (2.16)	4.41 (1.96)
95% CI	3.47, 4.01	3.74, 4.44	3.96, 4.86
Mean change (95% CI)	NA	0.42 (0.07, 0.77)	0.61 (0.20, 1.02)
Patch C			
Mean (SD)	1.10 (1.29)	0.99 (1.46)	1.11 (2.00)
95% CI	0.90, 1.30	0.75, 1.23	0.66, 1.56
Mean change (95% CI)	NA	−0.16 (−0.45, 0.13)	−0.08 (−0.57, 0.41)
Patch D			
Mean (SD)	0.38 (0.95)	0.38 (0.92)	0.60 (1.45)
95% CI	0.22, 0.54	0.22, 0.54	0.27, 0.93
Mean change (95% CI)	NA	−0.22 (−0.22, 0.18)	0.21 (−0.12, 0.54)
Patch E			
Mean (SD)	0.12 (0.44)	0.14 (0.62)	0.44 (1.21)
95% CI*	0.04, 0.20	0.04, 0.24	0.17, 0.71
Mean change (95% CI)	NA	0.02 (0.12, 0.16)	0.32 (0.05, 0.59)

* CI = confidence interval; NA = not applicable; SD = standard deviation.

over time for any of the corneal regions. Changes in cell density (Table 11) were within error of testing.

Subjective Evaluations. Extreme/marked or moderate improvement in postoperative vision was noted by 300 (85%) of 353 of patients at 1 month and by 313 (90%) of 347 at 12 months (Table 12). Ten patients (3%) thought they had no improvement at 12 months. Patients who were very satisfied or satisfied with the results of their surgery numbered 77% at 1 month and 81% at 12 months (Table 13).

Table 9. Mesopic Contrast Sensitivity with Glare

	Preoperative N = 158	Month 6 N = 141	Month 12 N = 73
Patch A			
Mean (SD)	3.61 (1.57)	3.83 (1.89)	4.14 (1.91)
95% CI*	3.36, 3.86	3.52, 4.14	3.71, 4.57
Mean change (95% CI)	NA	0.26 (−0.07, 0.59)	0.62 (0.19, 1.05)
Patch B			
Mean (SD)	3.27 (1.67)	3.51 (2.13)	4.19 (2.05)
95% CI	3.02, 3.52	3.16, 3.86	3.72, 4.66
Mean change (95% CI)	NA	0.24 (−0.11, 0.59)	0.93 (0.46, 1.40)
Patch C			
Mean (SD)	0.83 (1.11)	0.78 (1.30)	0.88 (1.75)
95% CI	0.65, 1.01	0.56, 1.00	0.49, 1.27
Mean change (95% CI)	NA	−0.10 (−0.37, 0.17)	−0.07 (−0.48, 0.34)
Patch D			
Mean (SD)	0.26 (0.73)	0.29 (0.95)	0.55 (1.38)
95% CI	0.14, 0.38	0.13, 0.45	0.24, 0.86
Mean change (95% CI)	NA	0.03 (−0.17, 0.23)	0.31 (0.02, 0.60)
Patch E			
Mean (SD)	0.13 (0.61)	0.11 (0.39)	0.47 (1.35)
95% CI*	0.03, 0.23	0.05, 0.17	0.16, 0.78
Mean change (95% CI)	NA	−0.04 (−0.18, 0.10)	0.31 (0.02, 0.60)

CI = Confidence interval; NA = not applicable; SD = standard deviation.

Table 10. Mean Endothelial Cell Density over Time

Region	Pre-Op	3 Months	6 Months	12 Months
Central	(n = 162)	(n = 127)	(n = 123)	(n = 42)
Mean	2686	2730	2727	2683
SD	160.9	163.7	153.6	163.2
Mid-Periphery	(n = 162)	(n = 111)	(n = 108)	(n = 31)
Mean	2722	2734	2727	2691
SD	162	141.3	134.4	158.4
Periphery	(n = 159)	(n = 107)	(n = 104)	(n = 28)
Mean	2724	2727	2724	2716
SD	150.9	140.2	138.4	145.3

SD = standard deviation.

Effects on the Cornea

Corneal Topography. Orbscan corneal topography, with a preoperative view (Fig 9A) and with the same cornea 1 year after CK treatment (Fig 9B), shows postoperative central corneal steepening surrounded by midperipheral flattening.

Slit Lamp. Fig 10 shows a slit-lamp photograph of the cornea 1 hour after CK treatment. The paired (6- and 7-mm OZs) treatment spots of thermal coagulation are visible as small surface leukomas, with lines of tension, or striae, connecting the treatment spots.

Histology. Histology views of the footprint in the corneal stroma of a pig's eye 1 week after treatment show the treatment effect penetrating to approximately 80% of the depth of the midperipheral cornea (Fig 11).

Confocal Microscopy. Confocal microscopy of a patient's eye 12 months after CK treatment (Fig 12) shows a prominent stromal fold in the striae between the two treatment spots. Fig 13 shows deep stromal penetration without damage to the corneal endothelium.

Discussion

Collagen protein maintains its spiral triple-helix configuration through the covalent bonds between its long chains and the hydrogen bonds between the molecules. These bonds are

Table 11. Changes in Endothelial Cell Density from Pre-op

Region	3 M	6 M	12 M
Central	(N = 127)	(N = 123)	(N = 42)
Mean (SD)	+0.31% (4.5)	+1.4% (4.2)	+1.0% (3.9)
CI	−0.57, 0.99	0.66, 2.1	−0.19 to +2.2
Mid periphery	(N = 111)	(N = 108)	(N = 31)
Mean (SD)	−0.61% (3.0)	−0.23% (3.05)	−0.6% (3.6)
CI	−1.2, −0.08	−0.8, 0.35	−1.87 (0.69)
Periphery	(N = 107)	(N = 104)	(N = 28)
Mean (SD)	−0.76% (2.9)	−0.41% (3.2)	0.2% (3.5)
CI	−1.3, −0.28	−1.03, 0.21	−1.1, 1.5

CI = confidence interval; SD = standard deviation.

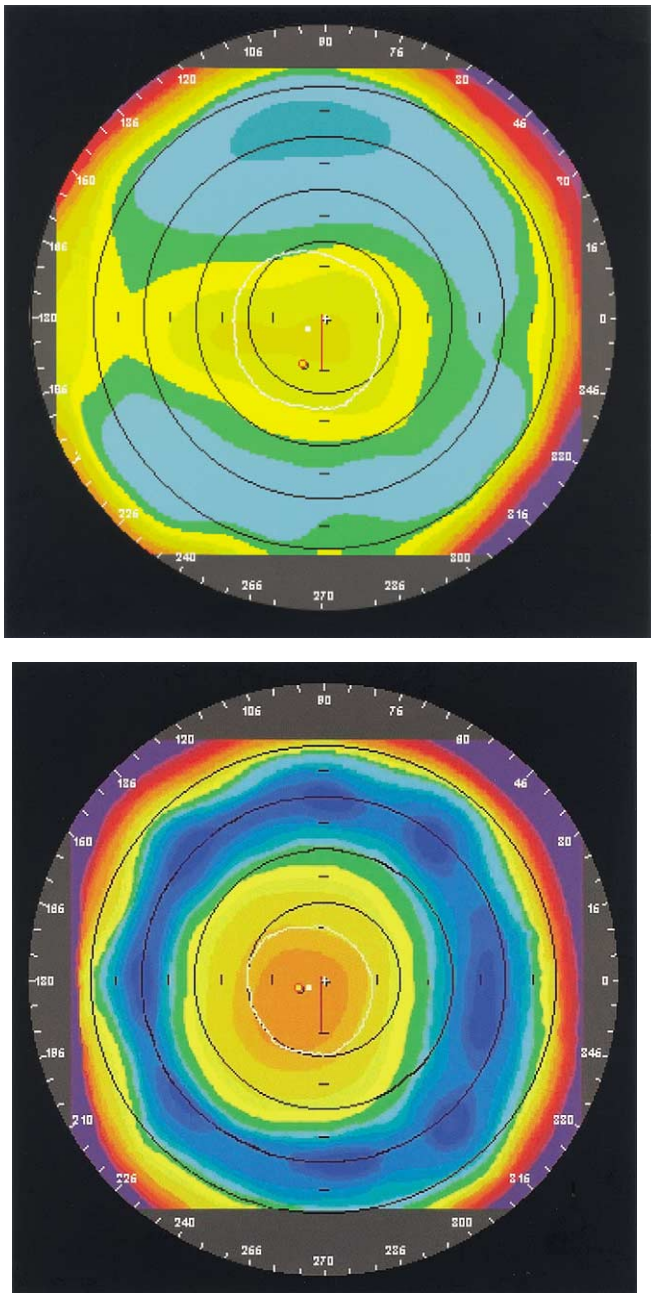


Figure 9. A, Orbscan preoperative topography of a conductive keratoplasty (CK)-treated eye. **B,** Orbscan postoperative topography of the same CK-treated eye 1 year after treatment. Orbscan images courtesy of Daniel Durrie, MD.

highly susceptible to disintegration from exposure to an increase in temperature and the duration of that increase.[29,30] Under steady-state laboratory conditions, collagen heated in the range of 55° C to 65° C dehydrates and contracts, but it can still regain its original configuration upon cooling. At >75° C, collagen denatures completely and turns into gelatin. Thus, under steady-state conditions, the temperature window for collagen contraction without complete denaturation is thought to be approximately 65° C to 75° C. However, because thermokeratoplasty is a dynamic (not steady-state) process, the state of collagen while it undergoes thermokeratoplasty can be inferred, but not exactly defined, through these steady-state temperature studies.

Table 12. Patient Evaluation of Vision Quality

Improvement	Month 1	Month 3	Month 6	Month 12
Extreme/marked	232/353 (66%)	246/361 (68%)	273/370 (74%)	260/347 (75%)
Moderate	68/353 (19%)	78/361 (22%)	57/370 (15%)	53/347 (15%)
Slight	37/353 (10%)	22/361 (6%)	28/370 (8%)	24/347 (7%)
None	16/353 (5%)	15/361 (4%)	12/370 (3%)	10/347 (3%)

CK generates heat in the cornea by using the electrical properties of corneal stromal tissue. Stromal tissue provides resistance to the flow of the current, resulting in controlled tissue heating and collagen coagulation. The process is self-limiting because resistance to the flow of the current increases with the increasing dehydration of collagen. According to a thermal model, the CK treatment zone reaches a temperature consistent with optimal shrinkage. Each treatment spot produces a cylindrical footprint that extends to approximately 80% of the depth of the midperipheral cornea (Goth P, Stern R, personal communication, 2000). The histology of a pig eye shows a footprint extending down to 80% of the midperipheral cornea after CK treatment[31] (Fig 11) and supports the thermal model. Because permanent contraction of collagen through thermokeratoplasty has been shown to depend on achieving a consistent, deep zone of collagen shrinkage,[32] deep penetration is desirable to minimize regression.

The CK procedure emits a consistent temperature along the depth of the probe. During energy application, the thermal effect proceeds from the point of the probe up the shaft (from the bottom, up) as it finds the path of least

Figure 10. Slit-lamp view of treatment spots 1 hour after conductive keratoplasty, showing bands of striae between spots. The surface leukomas are small because all of the energy is delivered within the stroma.

Table 13. Patient Satisfaction

Patient Response	Month 1	Month 6	Month 12
Very satisfied/satisfied	273/356 (77%)	306/371 (82%)	282/347 (81%)
Neutral	57/356 (16%)	34/371 (9%)	33/347 (10%)
Dissatisfied	16/356 (4%)	20/371 (5%)	25/347 (7%)
Very dissatisfied	10/356 (3%)	11/371 (3%)	7/347 (2%)

resistance. The result is a cylindrical thermal effect that has almost no axial component. Thus, a cylindrical footprint is made in the stroma. The small leukomas seen at CK-treated spots demonstrate that CK delivers energy deep into the stroma rather than on the surface. In contrast, the noncontact LTK technique generates the greatest amount of heat at the surface of the cornea because of the high absorption of light energy in water. The holmium:yttrium–aluminum–garnet beam is attenuated as it passes through the cornea so that the heat energy diffuses radially and axially into the tissue. The result is corneal denaturation decreasing from top to bottom, forming a cone-shaped zone of collagen shrinkage[33] of a depth that seems to be more shallow than that of a CK-treated spot.

In the multicenter clinical trial reported here, the efficacy results exceeded all FDA guidelines for performance of refractive surgery procedures. At 1 year after treatment, 56% of the study eyes showed 20/20 or better UCVA, and 92% showed 20/40 or better. Eyes were approximately 0.50 D myopic at month 1 and were effectively emmetropic at 6 months. At 1 year, the mean MRSE was within ±0.50 D in 63% and within ±1.00 D in 89%. These predictability values match or exceed those of other procedures for similar levels of hyperopia. During the last two intervals (6 to 9 months and 9 to 12 months), the cycloplegic refractive spherical equivalent refraction changed 0.11 and 0.11 D, respectively. Thus, the refraction seemed to stabilize by 6 months and to maintain a stable level through 1 year. This amount of change is similar to the natural progression of hyperopia in eyes that have not had refractive surgery. Because we performed no retreatments, our stability results reflect actual corneal refractive stability over the 1-year follow-up.

BSCVA was generally preserved after the procedure, and no eye had BSCVA worse than 20/40. The incidence of induced cylinder of ≥2.00 D was <1% (the FDA target is 5%). At 1 year, 6% showed a 1.00-D increase in cylinder, and 4% showed an increase of >1.00 D but <2.00 D. These percentages are clinically acceptable. This cylinder profile is similar to that of LTK, in which thermal spots are applied simultaneously to the cornea (Table 14). CK may owe its safety profile to the preservation of the visual axis in the procedure. In comparison, hyperopic photorefractive keratectomy[16–21] and hyperopic laser in situ keratomileusis studies[22–28] have demonstrated a two-line or greater loss of BSCVA of up to 6%. Furthermore, CK-treated eyes showed no loss of contrast sensitivity when tested with and without glare. This provides additional evidence of safety.

Although the incidence and level of haze seen at 1, 3, and 6 months after CK was low, none was expected. The haze that was observed might be attributed to one investigational center at which haze observed on any part of the cornea (including at the CK treatment site, which is expected to be hazy) was recorded instead of at the central cornea only.

Possible damage to the corneal endothelium after deep thermal penetration in the stroma by CK treatment was assessed from data collected on 162 eyes at 3 investigational sites. Cell counts taken before surgery and at 3, 6, and 12 months after surgery at the central cornea, the 3-mm OZ, and the 6-mm OZ showed no clinically or statistically significant changes from preoperative levels. Confocal microscopy views (Figs 12 and 13) also showed deep penetration without damage to the endothelium. Thus, the interim data seem to indicate that the CK procedure is safe for the corneal endothelium. Furthermore, no spikes were seen in postoperative IOP data, suggesting that flattening of the cornea by the procedure did not cause shallowing of the peripheral chamber angle.

Leucomas visible by slit lamp after surgery were small because CK delivers energy deep into the stroma rather than on the surface. The striae between treatment zones remained

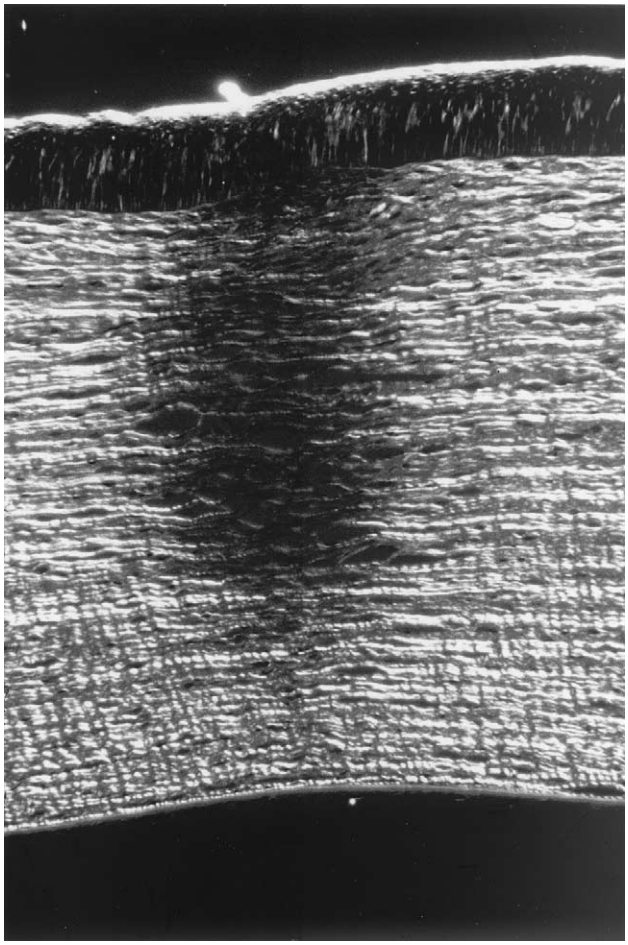


Figure 11. Histology view of a pig eye 1 week after conductive keratoplasty treatment, showing a cylindrical footprint and a treatment effect extending to 80% of the corneal depth.

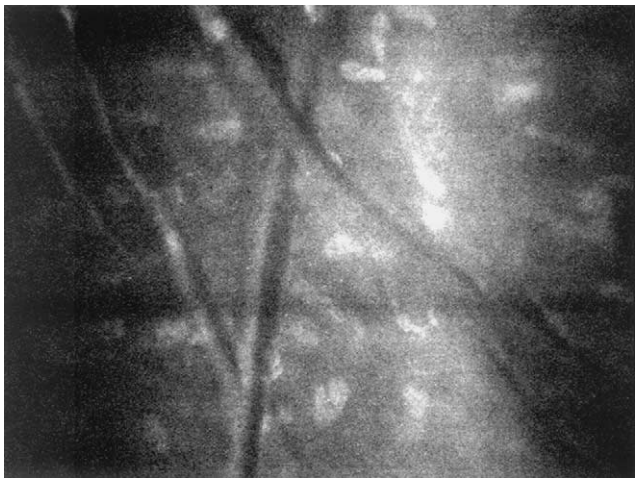


Figure 12. Confocal microscopy view of folds between conductive keratoplasty–treated spots.

visible at 12 months, as reported by the U.S. CK clinical trial investigators and as demonstrated by confocal microscopy; this suggests that the effect of treatment on the stroma is long-lasting. These persistent stromal effects would help to explain the refractive stability that has been seen after CK.

Subjective (patient) evaluations indicated high levels of satisfaction (very satisfied or satisfied: 76% at 1 month and 81% at 1 year) and a high subjective level of improvement in visual quality.

The CK technique seems to effectively correct low to moderate hyperopia in patients 40 years of age or older, produces stable results by 6 months, spares the visual axis, has an excellent safety profile, and does not involve removal of any corneal tissue or use of a microkeratome. The 2-year data from this ongoing trial should help to confirm the favorable 12-month findings.

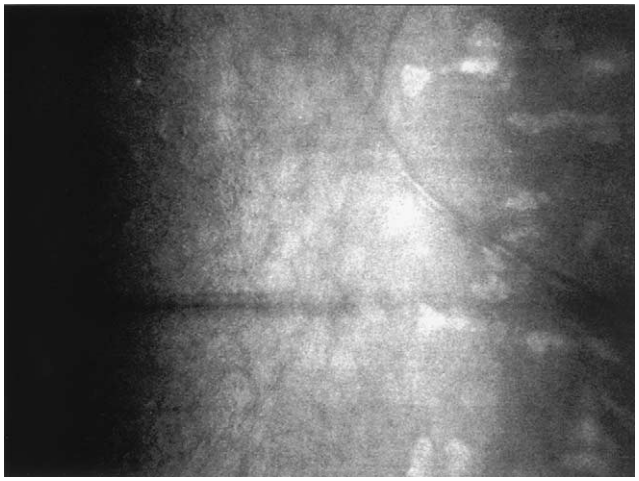


Figure 13. Confocal microscopy view of a conductive keratoplasty–treated spot, showing deep stromal penetration and a healthy endothelium.

Table 14. Induced Cylinder >2.00 D: Conducive Keratoplasty versus Non-contact Laser Thermal Keratoplasty

Post-op Month	LTK*	CK†
1 Month	3.4%	3.0%
3 Months	1.4%	2.0%
6 Months	0.9%	1.0%
12 Months	0.2%	0.3%

* Hyperion Non-contact Laser Thermal Keratoplasty (LTK) System Device Labeling, PMA P990078, Sunrise Technologies, Fremont, California, May 2000.

† Conductive Keratoplasty (CK) FDA Pre Market Approval data, November, 2001.

D = diopters.

Appendix

The following are members of the Conductive Keratoplasty United States Investigators Group: Penny Asbell, MD; Stephen Brint, MD; William Culbertson, MD; Elizabeth Davis, MD; Dan Durrie, MD; David Hardten, MD; Vera Kowal, MD; Richard Lindstrom, MD; Roger Meyer, MD; Thomas Samuelson, MD; Timothy Schneider, MD; Kaz Soong, MD; and Alan Sugar, MD.

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Discussion
by
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This study is potentially of great importance to refractive surgery for two reasons. First, it is the second large, well-designed clinical trial of thermal keratoplasty for treatment of hyperopia; the authors report on 95% follow-up in eyes available for 1-year evaluation. Second, it describes an intriguing nonlaser technology with a unique method of delivering energy into the corneal stroma. As the authors point out, the theoretical advantage of this technology is the more uniform application of heat throughout the 400-μm length of the needle, contrasted with the conical pattern of heat delivery achieved with nonpenetrating devices.

The authors' 1-year results are excellent in almost all regards, exceeding the Food and Drug Administration criteria for myopia correction for the categories of uncorrected visual acuity, predictability, and safety. Most importantly, none of the eyes experienced visual loss to 20/40 or worse.

There are several elements of the patient data that, if explored further, could increase our understanding of the applications of this technology.

1. It would be useful to learn the etiology of visual loss in the 2% of eyes that lost two lines of vision at 12 months. Was this because of irregular astigmatism? Can we learn something about these eyes from a careful analysis of their postoperative topography?
2. The major complication of this treatment seems to be surgically induced astigmatism. At 1 year after surgery, >10% of eyes had an arithmetic increase in their refractive astigmatism of 1 diopter (D) or more. Aggregate vector analysis would be helpful to better understand the magnitude of the induced cylinder and determine whether there is a preferred orientation of the induced cylinder.[1] One concern with using a handheld probe for multiple applications is that corneal properties change during the course of the treatment. It is conceivable that the cylinder is induced by the particular pattern used in this study and that adjustments in the energy delivered in each spot or in the pattern itself might reduce this problem.
3. The patient satisfaction data were again excellent overall, especially because there were no retreatments. However, it would be helpful to analyze the visual outcomes in the 9% of patients who were dissatisfied or very dissatisfied at 1 year after surgery.

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