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New method of microwave thermokeratoplasty to correct myopia in 33 eyes: One-year results

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PURPOSE: To assess the safety, predictability, and stability of a new microwave thermokeratoplasty procedure to correct myopia.

SETTING: Cornea and refractive surgery subspecialty.

DESIGN: Prospective clinical trial.

METHOD: Thermokeratoplasty was performed in myopic eyes at a single center in Turkey from June 2009 to June 2010. The attempted corrections ranged from −1.25 to −5.75 diopters (D). The main outcome measures were changes in logMAR uncorrected distance visual acuity (UDVA) and in keratometry (K) values.

RESULTS: The procedure was performed in 33 eyes (patients aged 20 to 45 years). The mean preoperative logMAR UDVA (0.76 ± 0.24 [SD]) significantly improved to 0.19 ± 0.20 at 1 month, postoperatively. By 3 months, the mean UDVA had markedly regressed to 0.59 ± 0.29; however, the residual improvement remained statistically significant. At 12 months, the mean logMAR UDVA was 0.72 ± 0.26. The mean K values were 43.9 ± 1.36 D preoperatively, 41.25 ± 2.63 D at 1 month, 43.4 ± 1.69 D at 3 months, and 44.1 ± 1.09 D at 12 months. The mean endothelial cell density was 2836 ± 342 cells/mm^2 preoperatively and were statistically unchanged 12 months postoperatively (2732 ± 353 cell/mm^2). No patient lost lines of corrected distance visual acuity by 12 months postoperatively.

CONCLUSIONS: The new thermokeratoplasty procedure produced the desired reduction in myopia and improvement in postoperative UDVA 1 month postoperatively without significant side effects. However, early and complete regression shows the need for further development of this technique.

Financial Disclosure: Drs. Yilmaz and Marshall are paid consultants to Avedro, Inc., and Dr. Muller is president and CEO of Avedro, Inc. No other author has a financial or proprietary interest in any material or method mentioned.

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At present, the most widely used surgical treatments for myopia are photorefractive keratectomy and laser in situ keratomileusis.[1] Both procedures have inherent disadvantages. Photorefractive keratectomy patients experience postoperative pain until the cornea reepithelializes, stabilization of the refractive correction over time, and haze.[2–8] Laser in situ keratomileusis has an attendant risk for ectasia.[9–17] Both procedures involve disruption of collagen fibers in the cornea due to ablation. As an alternative, methods that use thermal energy to modify the cornea have been attempted and are reported in several studies.[18–21] In these studies, the peripheral cornea was generally targeted and the heating affected the full thickness of the cornea. Furthermore, these methods did not show a predictable dose response between the energy and induced refractive change.

The aim of this study was to evaluate a new device and technique that involve the application of microwave energy to the superficial layers of the central cornea as a treatment for myopia.

PATIENTS AND METHODS

This prospective study was performed to evaluate a new microwave thermokeratoplasty procedure for the correction of myopia. The setting was the refractive surgery department of an academic hospital specializing in ophthalmology. The study was approved by the Ethics Committee, Beyoglu

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Eye Training and Research Hospital and was performed in accordance with the ethical standards set in the 1964 Declaration of Helsinki and renewed in 2000. All participants understood that the microwave-induced changes, being thermal, might be transitory and could be lost over time. After receiving a detailed explanation of the study's purpose and procedures, all participants provided written informed consent. Patients had the procedure from June 2009 to June 2010.

The primary inclusion criteria were myopia, age older than 18 years, a corrected distance visual acuity (CDVA) of 20/25 or better in each eye, and a stable refraction (0.5 diopter [D] or less change in spheroequivalent) for at least 1 year.

Patients were not included if they had any of the following: a history of intraocular or corneal surgery, a history of systemic disease or use of systemic medication likely to affect corneal wound healing, anterior segment pathology, residual or active ocular disease, or a history of herpes keratitis. Patients were also not included if corneal topography images showed keratoconus, pellucid marginal degeneration, or other corneal pathologies.

The main outcome measures were changes in logMAR uncorrected distance visual acuity (UDVA) and in keratometry (K) values.

All eyes were examined preoperatively and 1 week, 1 month, 3 months, 6 months, and 12 months postoperatively. Examinations included measurement of UDVA and CDVA (Vision Tester 6500), slitlamp biomicroscopy, Goldmann applanation tonometry, corneal topography (Pentacam, Oculus, Inc., and Orbscan II, Vision System, Inc.), central pachymetry, endothelial cell count (ECC), and fundus examination.

Postoperative anterior stromal haze was graded according to the scale described by Nakamura et al.[22] as follows: 0 = clear; 0.5 = faint corneal haze; 1 = mild corneal haze seen only with oblique indirect illumination; 2 = moderate corneal haze seen with direct illumination; 3 = easily visible opacity not affecting refraction; 4 = dense opacity impairing the view of intraocular structures, possibly affecting refraction.

Device Description

The Avedro Vedera KXS system consists of a radiofrequency-generating device, control console and articulated arm, a targeting stage with a suction ring, a treatment applicator, and 2 disposable items (a reticule and a sterile preservative coat for treatment applicator) (Figure 1). Treatment radiofrequency power is provided by a microwave amplifier housed in the body of the device. To ensure dose precision, power sensor assemblies were provided to measure forward and reflected power. The device contains a 2-part vacuum system. One phase of the vacuum system was used to couple the vacuum stage to the eye with vacuum adjustable up to −680 nm Hg, relative to ambient pressure (80 mm Hg absolute). This phase remained turned on throughout the procedure. The second phase of the vacuum system released a movable platform within the targeting stage to be positioned over the corneal apex with the aid of a removable reticule before being locked in position by application of vacuum. The treatment applicator was designed to couple tightly within the targeting stage, coaxial to the alignment reticule. The treatment applicator consisted of concentric inner and outer annular electrodes, which provided for delivery of an annulus of microwave energy to the cornea and which enclosed conduits for coolant dispersal onto the corneal surface. Feedback-controlled motors positioned the electrodes in the *z*-plane for coupling the electrodes to the corneal tissue. A disposable flexible membrane covered the electrodes, isolated the eye from direct exposure to the coolant, and provided a sterile interface to the patient's eye. A typical treatment was 30 to 100 W of microwave power at a frequency of 915 MHz, with a pulse duration of 10 to 60 milliseconds. Total energy to the eye was in the range of 4 to 20 J. The total pulse of power was between 1/100th and 1/10th of a second. The suction ring and positioning brake vacuum, along with electrical power for illumination, were provided via a sterile single-use vacuum tubing set. A 50-millisecond pulse of cooling agent was applied before the heating microwave pulse, and then further pulses (10 to 60 ms) were provided throughout the microwave emission. The goal of cooling was to cool the surface of the eye adequately to minimize epithelial damage while being balanced with the microwave heating pulse to shrink collagen just below the surface of the cornea. Histologic evidence shows that collagen alterations are limited to a depth approximately 200 μm below the surface, without significant discontinuities in collagen structure.[23] In addition, theoretical modeling shows that microwave powers above 100 W are required to result in significant regions of tissue heating above 80°C.[24]

The dose regimen, power, and time varied between eyes and depended on the magnitude of the refractive error. The dose-effect dependence was derived from extensive laboratory studies of animal and human corneas together with computer modeling.[23]

Surgical Technique

The patient details, including treatment requirements, were entered into the control console. A drop of pilocarpine 2.0% was instilled in the eye 30 minutes before the procedure. After a drop of proparacaine hydrochloride (Alcaine) was applied, a wire lid speculum was used. To centralize the annular electrodes, the corneal apex was located using the first Purkinje image as a reference. The first Purkinje reflex was marked with a Sinskey hook while the patient fixated on the light source of the operating microscope. This provided approximate alignment with the visual axis. The targeting stage was positioned on the eye, and the vacuum was activated to lock the targeting stage in place while allowing movement of the inner targeting element. A cross-hair target reticule was inserted into the targeting stage

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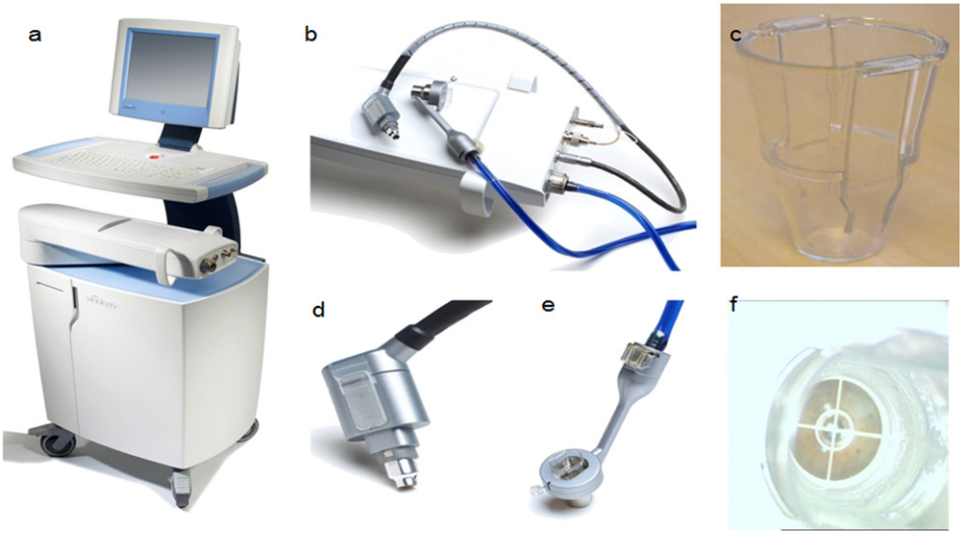

Figure 1. *A*: Microwave thermokeratoplasty device. *B*: Articulating arm with targeting stage and applicator. *C*: Reticule. *D*: Treatment applicator. *E*: Targeting stage. (*F*) Reticule coupled with targeting stage.

and was manually positioned over the previously marked first Purkinje reflex on the cornea. The targeting stage was then locked in place by the second vacuum phase, and the reticule was removed. The microwave applicator was inserted into the targeting stage and then properly seated; the physician depressed a foot switch to initiate the automated sequence of electrode coupling, cooling, and treatment pulses, thereby delivering treatment energy to the cornea. After the application was completed, the vacuum to the targeting stage was automatically uncoupled, detaching the targeting stage and applicator from the eye. These were removed before loose epithelium and debris were cleared from the surface with a Weck-Cel sponge (Medtronic Xomed, Inc.). A bandage contact lens was inserted. Finally, the lid speculum was removed from the eye. The entire procedure typically took 25 to 35 seconds from the first phase of vacuum application to the end of the procedure (mean duration 28.66 seconds ± 3.61 [SD]).

Tetracaine 0.5% eyedrops 8 drops per day immediately after the procedure, moxifloxacin 0.5% eyedrops (Vigamox) 4 drops per day immediately after the procedure and every day for 1 week thereafter, and artificial tears 4 drops per day for 1 month were prescribed. Verma et al.[25] and Brilakis and Deutsch[26] found that the use of tetracaine in refractive surgery procedures did not prolong the time to reepithelialization. Providing patients with a limited amount of tetracaine (only on the day of surgery) prevented abuse and toxicity to the cornea while managing pain. Medications that included corticosteroids were not used.

Statistical Analysis

Statistical analyses were performed with SPSS for Windows software (version 11.5, SPSS, Inc.). Preoperative and postoperative data were compared using the paired-samples *t* test. For visual acuity evaluation, Snellen scale values were transformed to logMAR notation. Differences were considered statistically significant when the *P* value was less than 0.05.

RESULTS

The procedure was performed in 24 right eyes (72.7%) and 9 left eyes (27.3%) of 33 patients (15 men, 18 women). The mean age of the patients was 27.3 ± 7.05 years (range 20 to 45 years). The mean attempted correction was −3.13 ± 1.31 D (range −1.25 D to −5.75 D).

All 33 patients returned for the postoperative follow-up visits at 1 day, 1 week, and 1 month. Attendance decreased to 31 patients at 3 months, 25 patients at 6 months, and 19 patients at 12 months.

All eyes that had the procedure had a mild annular area of disrupted epithelium that corresponded to the area over which the electrode was applied. This annulus, which measured approximately 400 µm from the inner diameter to outer diameter, could be seen as a ring of mild haze (grade 1); in all patients, this reepithelialized 1 day postoperatively (Figure 2). In all eyes, the annular haze diminished during the first postoperative month. Mild associated changes were seen on slitlamp examination in the following months. At the 6-month visit, there was faint stromal haze (grade 0.5) or no stromal haze (grade 0). Figure 3 shows the attempted correction versus the achieved correction at 1 month in the 33 eyes. The plot shows a linear relationship between −1.00 D and −5.75 D. With the exception of 3 eyes, all data fell within the linear zone predicted by the algorithm.

The mean preoperative UDVA was 0.76 ± 0.24 logMAR (range 0.30 to 1.30 logMAR) and the mean preoperative CDVA, 0.00 ± 0.06 logMAR (range −0.08 to 0.40 logMAR). Preoperatively, the mean K value was 43.90 ± 1.36 D (range 41.6 to 46.55 D), the mean manifest refraction spherical equivalent (MRSE) was −2.92 ± 1.42 D (range −5.75 to −1.25 D), and the mean central corneal thickness measured by ultrasound pachymetry was 556 ± 39.8 µm (range 487 to 647 µm). The mean ECC was 2836 ± 342 cells/mm^2 (range 2020 to 3521 cells/mm^2), and the mesopic pupil diameter was 5.81 ± 1.1 mm (range 3.00 mm to 7.00 mm).

Figure 2. Postoperative eye on the day of surgery.

Figure 4 shows the changes in the mean and distribution of the UDVA and CDVA during the study period. The mean UDVA was significantly improved 1 week (0.21 ± 0.16 logMAR; $P<.001$) and 1 month (0.17 ± 0.18 logMAR; $P<.001$) postoperatively. Although a marked regression was observed at 3 months (mean 0.57 ± 0.27 logMAR; $P=.001$), the improvement was still statistically significant compared with the preoperative mean. There was no significant difference in the mean UDVA at 6 months (0.68 ± 0.19 logMAR; $P=.139$) or at 12 months (0.72 ± 0.26 logMAR; $P=.444$). As the study continued, fewer patients remained; therefore, for comparisons of later visits and earlier visits, the means of the earlier visits were calculated only from patients who continued in the study.

Figure 5 shows the change and distribution in the mean MRSE. The mean preoperative MRSE decreased to 0.02 ± 1.77 D 1 week postoperatively ($P<.001$). It was −0.42 ± 1.42 D at 1 month ($P<.001$), −2.33 ± 1.48 D at 3 months ($P=.025$), −2.60 ± 1.14 D at 6 months ($P=.316$), and −2.86 ± 0.81 D at 12 months ($P=.225$). (All P values define comparisons with the preoperative mean.)

The mean cylinder in the eyes that had treatment was −0.12 ± 0.39 D preoperatively. This increased to a mean of −0.87 ± 0.76 D 1 week postoperatively ($P<.001$) and then began to decrease as follows: −0.68 ± 0.68 D at 1 month ($P<.001$), −0.29 ± 0.53 D at 3 months ($P=.039$), −0.29 ± 0.49 D at 6 months ($P=.044$), and −0.11 ± 0.33 D at 12 months ($P=.403$). (All P values here represent comparisons with the preoperative mean.) Figure 6 shows the distributions and changes in cylinder values. Cylinder values and CDVA had a negative correlation 1 week, 1 month, 3 months, and 6 months postoperatively in Pearson correlation analyses (Table 1). Although a small decrease in the mean CDVA was observed 1 week postoperatively (0.06 ± 0.09 logMAR; $P<.001$), no significant changes from preoperative values were present at 1 month (0.02 ± 0.09 logMAR; $P=.120$), 3 months (0.02 ± 0.08 logMAR; $P=.118$), 6 months (0.02 ± 0.04 logMAR; $P=.122$), or 12 months (0.01 ± 0.03 logMAR; $P=1.00$) (Figure 4). No eye lost lines of CDVA by the end of the 12-month follow-up (Figure 7).

The mean K value preoperatively was 43.9 ± 1.36 D. Postoperatively, it was 40.20 ± 3.13 D at 1 week ($P<.001$), 41.25 ± 2.63 D at 1 month ($P<.001$), 43.40 ± 1.69 D at 3 months ($P=.015$), 43.70 ± 1.50 D at 6 months ($P=.105$), and 44.10 ± 1.09 D at 12 months ($P=.741$) (Figure 8).

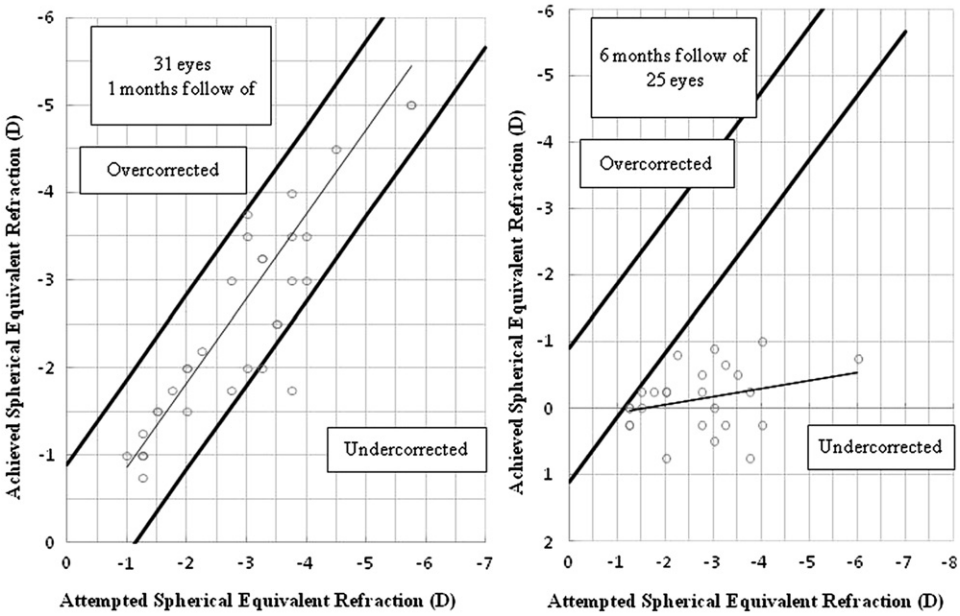

Figure 3. Attempted versus achieved MRSE correction 1 month and 6 months after treatment. The solid line represents the linear fit to the data. The dashed lines represent ±0.50 D of the mean.

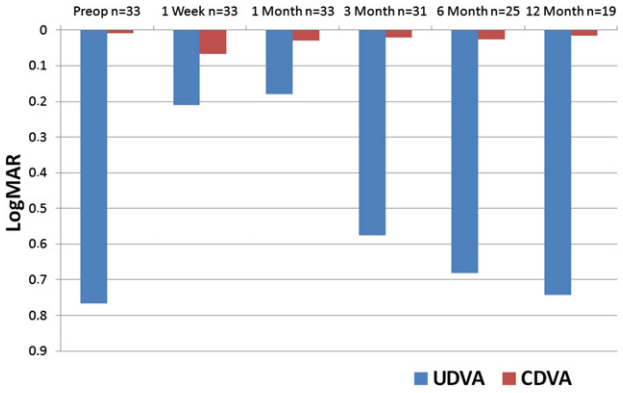

Figure 4. The change in UDVA and CDVA (CDVA = corrected distance visual acuity; UDVA = uncorrected distance visual acuity).

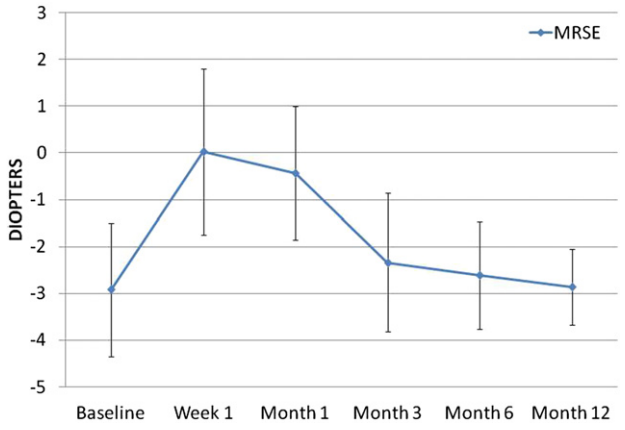

Figure 5. Change in mean MRSE over time (MRSE = mean refraction spherical equivalent).

The mean endothelial cell density was 2836 ± 342 cells/mm^2 preoperatively and 2732 ± 353 cells/mm^2, 12 months postoperatively. The difference was not statistically significant (P=.722).

Figure 9 shows a representative refractive power image derived from a Scheimpflug system. The characteristic central flattening is shown.

DISCUSSION

Previous studies of thermal procedures for changing the refractive properties of the cornea[27–30] found poor, if any, predictability between dose and response. In the present study, Figure 3 shows that even with the initial algorithm, such a predictive relationship has been established. It shows excellent precision, with 85% of eyes falling within ±0.50 D of the achieved correction. Given that the algorithm was based on in vitro empirical studies together with computer modeling, improvement in the treatment algorithm toward emmetropia should be a relatively fast process. The linearity of the dose-response curve between −1.00 D and −5.75 D is particularly noteworthy for a thermally based procedure.

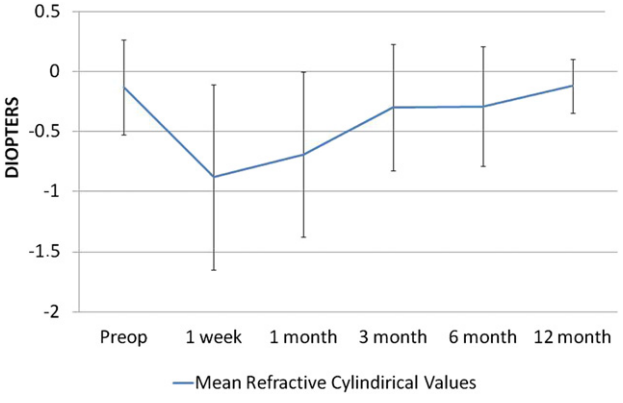

Figure 6. Change in mean cylinder over time.

The improvement in UDVA between baseline and the end of the first month after surgery is consistent with a procedure based on changing the length of the collagen fibrils by heat; however, the progressive reduction in the induced effect between 1 month and 3 months was disappointing and unexpected in its rapidity. Of note, in eyes with regression, subjective refraction and visual acuity regressed to baseline rather than regressing to some intermediate or distorted value (hyperopic shift or induced astigmatism). Although the mechanism of regression is not clear, we postulate that the regression is caused by a healing mechanism or that the volume of the affected stroma is insufficient to support the correction without eventual stress relaxation.

Because this method does not sever collagen fibers, it should provide refractive change without requiring loss of corneal stroma. Previous studies[31,32] found that if the temperature of collagen is raised above 60°C, the fibers undergo a degree of shrinkage and reformation, resulting in modification of the corneal curvature. When heated in excess of 78°C, collagen fibers start to degrade; the fiber structure is denatured above 100°C.[33] This process has been performed with contact lasers and noncontact lasers as well as with radiofrequency and microwave energy and has been shown to be an effective method of flattening the cornea.[31]

In other thermal radiofrequency procedures, the thermally induced refractive changes typically lasted for months.[27–30] Such procedures involved thermal transience passing through the entire corneal stroma, thus affecting a relatively large volume across adjacent lamellae. In contrast, the present technique applies a very mild change to the superficial corneal stroma, rarely penetrating greater than 200 to 250 µm. Previous studies using X-ray diffraction and measurements of cornea biomechanics[34–38] found that the superficial one third of the corneal stroma was where most of the strength of the system was located. It was hoped

Table 1. Correlation analyses between postoperative mean cylinder and mean CDVA values.

Parameter	Preoperative	Postoperative				
		1 Wk	1 Mo	3 Mo	6 Mo	12 Mo
Mean cylinder (D)	−0.128	−0.878	−0.689	−0.298	−0.290	−0.117
Mean CDVA (LogMAR)	−0.009	0.067	0.029	0.024	0.025	−0.012
r value	0.000	−0.374*	−0.445*	−0.341*	−0.321*	0.001
P value	1.000	0.032	0.009	0.043	0.041	0.997

CDVA = corrected distance visual acuity; *r* value = Pearson correlation
*Inverse correlation significant between cylinder and CDVA values

that by changing this layer only, there would be a maximum effect on refraction with little, if any, effect on corneal rigidity. Clearly, in the eyes in the present study, some remodeling of the tissue occurred, leading to loss of the initially induced refractive change and at a faster rate than those previously published for thermal keratoplasty. Further study is required to optimize the location, mechanism, and magnitude of microwave-induced effects to explore the possibility of sustaining the induced refractive change for long periods.

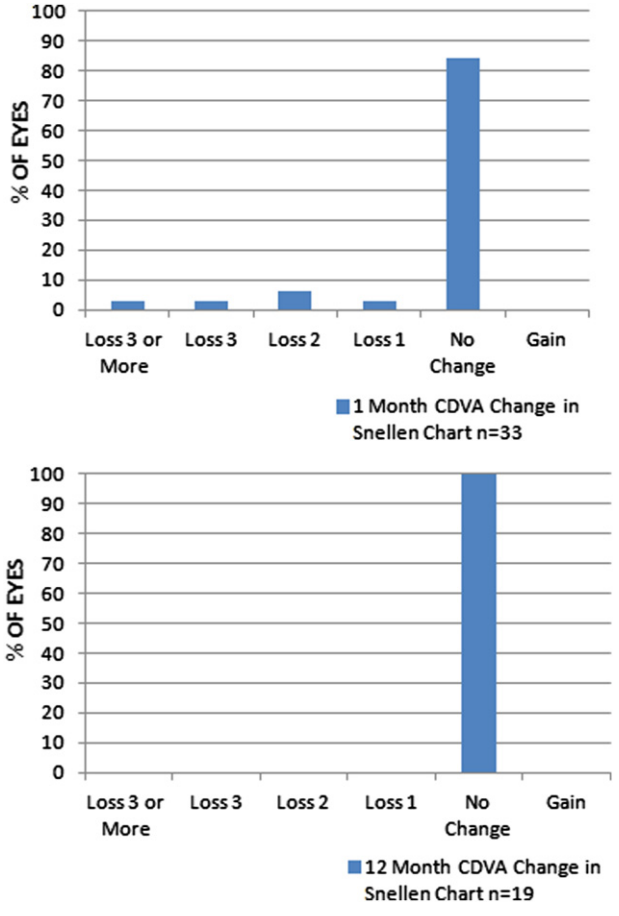

Figure 7. Change in mean CDVA over time (CDVA = corrected distance visual acuity).

Another approach to the transience of induced effect is to explore the use of riboflavin and ultraviolet radiation to crosslink the system and thus "freeze" or lock-in the microwave-induced changes.[39,40] Kymionis et al.[41] evaluated the combined effect of conductive keratoplasty (CK) followed by corneal collagen crosslinking in 2 keratoconus patients. Significant corneal topographic improvement was seen immediately after CK; however, the effect regressed during the first 3 months postoperatively and then remained stable, with no further changes noted in the sixth postoperative month in either patient. The results in that study, however, might not be directly comparable to those in our study given the differences in the number of patients, in the refractive conditions treated (keratoconus versus myopia), and in the treatment procedures that were used.

The procedure in the present study was safe with no significant side effects in CDVA or ECC over 12 months postoperatively. The loss of more than 1 line of CDVA at 1 week and 1 month and the lack of CDVA improvement at any time were correlated with induced astigmatism native in these patients; higher induced astigmatism was associated with poorer CDVA. Furthermore, given that the procedure

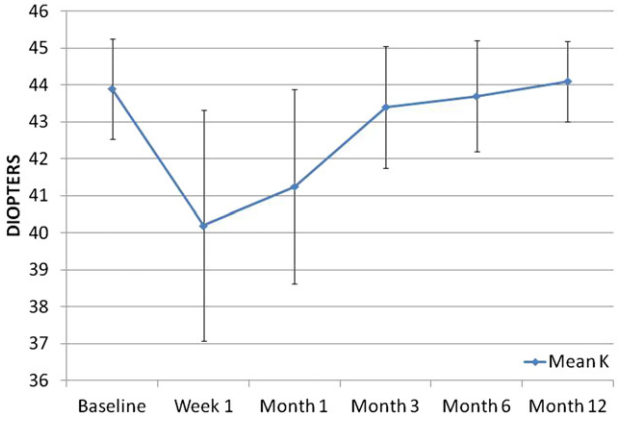

Figure 8. Change in mean keratometry values over time (K = keratometry result by Scheimpflug topography).

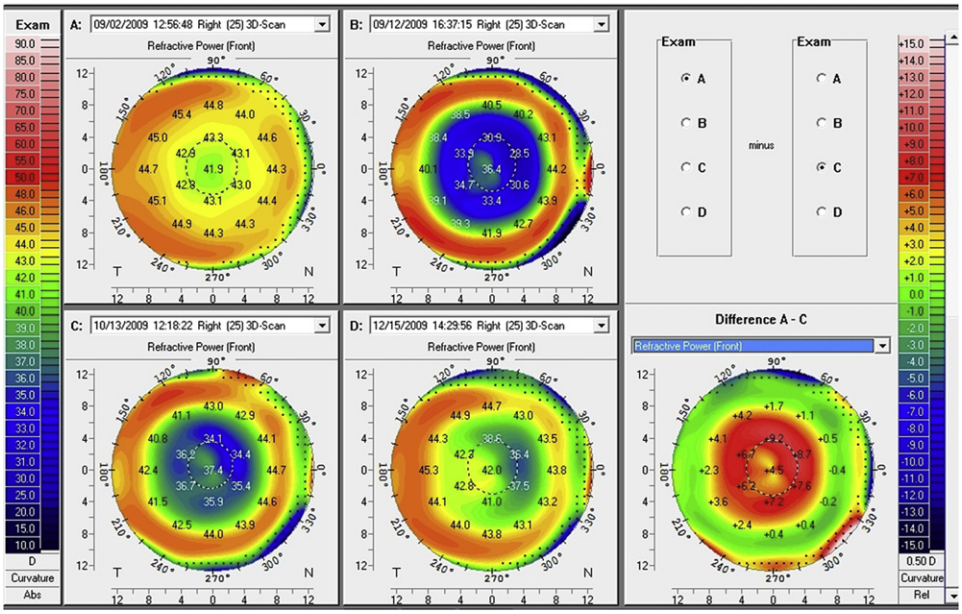

Figure 9. Scheimpflug refractive power images of 1 patient. *A*: Preoperative. *B*: One week. *C*: One month. *D*: Three months and difference map.

involves no removal or cutting of tissues, one would expect no weakening in the biomechanical parameters of the globe after surgery. The UDVA improved in all patients; however, the correction was not sustained. An important limitation of this study was the decrease in the number of participants over the follow-up.

An advantage of the current treatment is seen in the Pentacam image (Figure 9), which shows a prolate preoperative cornea that is still prolate postoperatively. This is in contrast to other techniques that remove tissue and therefore induce different optical zones with acute borders. The technique effectively has no zone that could be considered a classic optical zone because it retains all tissue in the stroma with the same refractive indices and refractive properties. Thus, the system appears to resemble a normal unoperated cornea but with improved optical properties.

Further work is required to optimize the temperatures applied to the epithelium during the treatment given the mild immediate postoperative changes that were seen and that disappeared by 1 day postoperatively. These epithelial responses imply that the cooling regimen before or during microwave application was insufficient to retain epithelial integrity.[42] However, in some eyes, only the superficial layers of the epithelium were disturbed, suggesting that mild modifications could lead to no epithelial damage.

In conclusion, the present study found that through a new device, microwave treatment achieved correction increases predictably in proportion to the applied energy, as reflected in the 1-month outcomes. The procedure appears to be safe, with no collateral effects on corneal transparency or endothelial cells. Microwaves provide an interesting modality for future applications in relation to corneal disease because refractive errors can be corrected without tissue loss. However, the early and complete regression of the treatment effect in this study shows the need for further development of this technique.

WHAT WAS KNOWN

- All ablation procedures are dependent on removal of tissue and thus change the biomechanical properties of the cornea.
- Thermal methods can provide refractive correction; however, the degree of correction has been unpredictable in previous studies.

WHAT THIS PAPER ADDS

- We describe a new device and technique that involves the application of microwaves to the corneal surface to change the refractive state of the cornea by changing the pathway and thereby the curvature of the collagen fibers, but without transecting them.
- Although the change in refraction was predictable, the changes were temporary, regressing over the course of 3 months.

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