New microwave thermokeratoplasty and accelerated crosslinking method for keratoconus: Results in 24 eyes during a 1-year follow-up

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PURPOSE: To evaluate the safety and efficacy of a new microwave thermokeratoplasty procedure combined with accelerated corneal collagen crosslinking (CXL) to improve visual function in patients with keratoconus.

SETTING: Cornea and refractive surgery department, Istanbul, Turkey.

DESIGN: Prospective clinical trial.

METHODS: Patients with keratoconus who had the combined procedure were evaluated over 12 months postoperatively. The main outcome measures were changes in logMAR uncorrected (UDVA) and corrected (CDVA) distance visual acuities and in keratometry (K) values.

RESULTS: The study enrolled 24 eyes of 24 patients aged 18 to 45 years. The attempted corrections ranged from −1.60 to −6.50 diopters (D). The mean preoperative UDVA of 0.66 logMAR ± 0.26 (SD) significantly improved to 0.39 ± 0.21 logMAR 1 month postoperatively. However by 6 months, the mean UDVA had regressed to 0.58 ± 0.21 logMAR. At 12 months, the mean UDVA was 0.62 ± 0.17 logMAR. The mean K value was 49.11 ± 2.43 D preoperatively, 43.50 ± 3.04 D 1 month postoperatively, 47.52 ± 2.99 D at 6 months, and 48.37 ± 3.00 D at 12 months. There were no cases of significant endothelial cell loss or loss of CDVA lines at 12 months.

CONCLUSIONS: The new thermokeratoplasty procedure followed by accelerated CXL produced the desired reduction in K values and improvement in postoperative UDVA without significant side effects. However, the early and complete regression of the thermokeratoplasty effect shows the need for further advancement of this technology.

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Keratoconus is a progressive ectatic disease of the cornea. Currently available options for the treatment of keratoconus include eyeglasses, contact lenses, intrastromal corneal ring segment implantation, and corneal collagen crosslinking (CXL).[1,2] Recently, accelerated corneal CXL was introduced to decrease the treatment time and has been proposed for use in combination with laser in situ keratomileusis (LASIK) to reduce the risk for post-LASIK ectasia.[3]

Corneal CXL is the only available treatment shown to increase corneal biomechanical strength and inhibit the progression of ectatic disease. Although stabilization of the cornea is of substantial benefit to patients with progressive ectatic disease, visual function remains limited after CLX in eyes with advanced keratoconus.

Experimental studies of microwave thermokeratoplasty have been published. In this treatment, axial

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shrinkage of the stromal collagen results in a change in corneal shape and as a consequence, alters the refractive power of the cornea.[4,5] We previously reported the clinical outcomes of this procedure in a long-term study of 33 patients with myopia.[6] In a pilot clinical study, Vega-Estrada et al.[7] evaluated the results of combined microwave thermokeratoplasty and accelerated CXL in patients with keratoconus. The goal of this intervention was to stabilize the outcome of the thermokeratoplasty by increasing the stiffness and biomechanical stability of the stroma with accelerated CXL.

The objective of the present study was to evaluate the efficacy and long-term stability of thermokeratoplasty combined with accelerated CXL in reducing the refractive error in eyes with keratoconus.

PATIENTS AND METHODS

This prospective study evaluated the outcomes of microwave thermokeratoplasty for refractive correction in patients with keratoconus at Beyoglu Eye Training and Research Hospital, Istanbul, Turkey. The surgeries were performed from January to June 2010. The hospital's ethics committee approved the study, which was performed in accordance with the ethical standards in the 1964 Declaration of Helsinki as renewed in 2000. All patients were informed that the thermal changes induced by the microwave technology might be transitory and could be lost over time. After receiving a detailed explanation of the study's purpose and procedures, all patients provided written informed consent.

Individuals 18 years and older with a diagnosis of progressive keratoconus were recruited for inclusion in the study. Progressive keratoconus was described as keratoconus progression confirmed by subjective loss of 1 or more lines of corrected distance visual acuity (CDVA) or a 1.0 diopter (D) or more increase in the maximum keratometry (K) value verified by repeated corneal tomography over at least 6 months, a maximum K value of less than 65.0 D, and a central corneal thickness of at least 400 μm in the eye to be treated. Patients were excluded from the study if they had any of the following: history of intraocular or corneal surgery, history of systemic disease or use of systemic medication likely to affect corneal wound healing, anterior segment pathology, residual or active ocular disease, and a history of herpetic keratitis or other corneal pathologies. The main outcome measures were changes in logMAR uncorrected distance visual acuity (UDVA), logMAR CDVA, and K values.

All eyes were examined preoperatively and postoperatively at 1 week and 1, 3, 6, 9, and 12 months. Examinations included the following evaluations at appropriate timepoints: UDVA and CDVA (Vision Tester 6500, Stereo Optical Co. Inc.), slitlamp biomicroscopy, Goldmann applanation tonometry, corneal topography (Pentacam, Oculus Optikgeräte GmbH and Orbscan II, Vision Systems, Inc.), ultrasound central pachymetry, endothelial cell count, and fundus evaluation.

Postoperative anterior stromal haze was graded according to the scale described by Nakamura et al.[8] 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; and 4 = dense opacity impairing the view of intraocular structures and possibly affecting refraction.

Surgical Technique

The surgery was performed in 2 stages. First, microwave thermokeratoplasty was performed using a radiofrequency-generating device (Vedera KXS, Avedro, Inc.). Accelerated CXL was performed immediately after completion of the thermokeratoplasty procedure.

Microwave Thermokeratoplasty The microwave thermokeratoplasty was performed using the radiofrequency-generating device as previously described in detail.[6] In brief, the radiofrequency power of the treatment was provided by a microwave amplifier housed in the body of the device. 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 that enclosed conduits for coolant dispersal onto the corneal surface. 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.

The patient's details, including treatment requirements, were entered into the control console. The dose regimen, power, and time varied among 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.[6,9,10]

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 an 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 but to allow movement of the inner targeting element. A crosshair target reticule was inserted into the targeting stage and was manually positioned over the previously marked first Purkinje reflex on the cornea.

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Avedro device provided by Avedro, Inc., Boston, Massachusetts, USA.

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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 when 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. The electrode annulus measured approximately 400 μm in width from inner to outer diameters and was positioned centrally on the cornea. After the application was complete, the vacuum to the targeting stage was automatically uncoupled, resulting in detachment of the targeting stage and applicator from the eye. These were removed before loose epithelium and debris were cleared from the surface with a cellulose sponge (Weck-Cel).

Collagen Crosslinking After completion of the thermokeratoplasty procedure, the crosslinking device was programmed for the accelerated CXL treatment. After proparacaine hydrochloride drops were applied, the corneal epithelium was removed with a 9.0 mm diameter blunt spatula. A drop of riboflavin solution 0.1% (Vibex 0.1%) was instilled, and additional drops were applied to the corneal bed at a rate of 1 drop every 2 minutes for 15 minutes. The patient was aligned under the radiofrequency-generating device and the cornea was exposed to 30 mw/cm^2 irradiation for 3 minutes, for a total dose of 5.4 J/cm^2. At the end of the procedure, a bandage contact lens was placed and the lid speculum was removed from the eye. Postoperative care included moxifloxacin 0.5% eyedrops (Vigamox) 4 times a day for 1 week and artificial tears 4 times a day for 1 month.

Statistical Analysis

Statistical analyses were performed using SPSS for Macintosh software (version 20.0, International Business Machines Corp.) The mean, standard deviation, frequency, and percentage were used for descriptive statistics. Variable distributions were checked with the Kolmogorov-Smirnov test. Student *t* tests were used to compare quantitative data. Repeated-measures analysis of variance with Bonferroni corrections were used for the repeated-measurement analysis. For visual acuity evaluation, Snellen scale values were converted to logMAR notation. Differences were considered statistically significant when the *P* value was less than 0.05.

RESULTS

Twenty-four keratoconus eyes (12 right eyes, 12 left eyes) of 24 patients were included in the study. The mean age of 13 men and 11 women was 28.41 years ± 9.15 (SD) (range 18 to 45 years). The mean attempted refractive correction was −3.90 ± 1.44 D (range −1.60 to −6.50 D). All patients completed the scheduled follow-up examinations.

The entire microwave thermokeratoplasty procedure (from first phase of vacuum application to the end of treatment) typically took 25 to 35 seconds (mean duration 28.66 ± 3.61 seconds).

All eyes 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 in width from inner to outer diameters, could be seen as a ring of mild haze (grade 1); however, reepithelialization occurred by 4 days postoperatively in all cases (Figure 1). In all eyes, this annular haze diminished during the first postoperative month. The associated changes seen on slitlamp examination were mild during the following months; at the 6-month visit the stromal haze was faint (grade 0.5).

Table 1 shows the changes in mean UDVA, CDVA, and MRSE over time. The mean UDVA was statistically significantly better 1 month postoperatively than preoperatively ($P < .001$). However, a marked regression was observed at 6 months ($P = .142$). There was no significant difference in the mean UDVA after

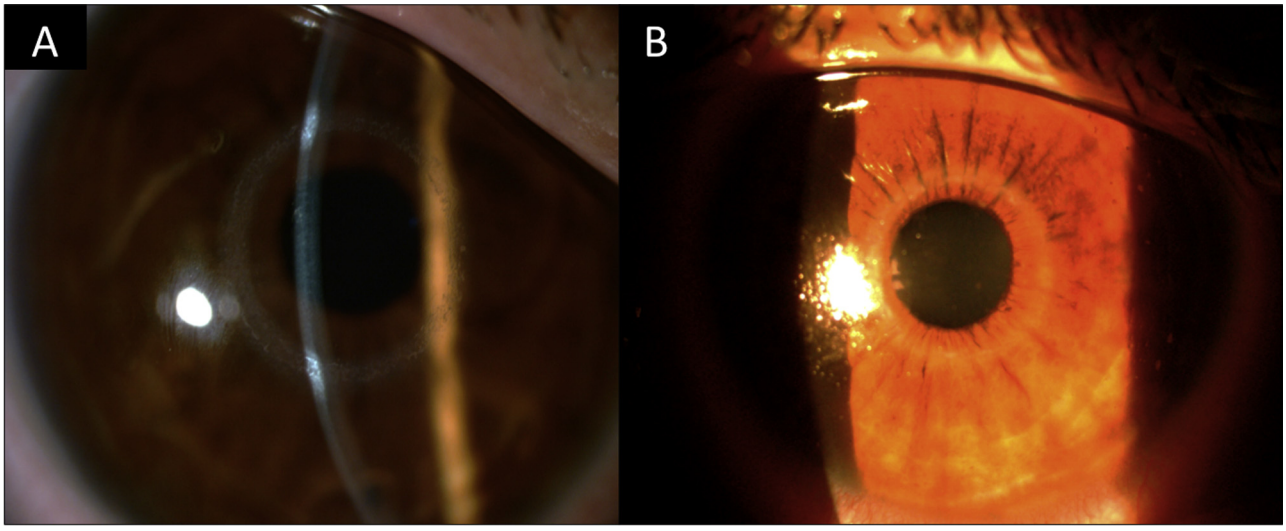

Figure 1. *A*: Photograph taken 4 days postoperatively. *B*: Photograph taken 1 month postoperatively.

Table 1. Refractive results.

	Preoperative	Postoperative									
		1 Month		3 Months		6 Months		9 Months		12 Months	
Parameter	Mean ± SD	Mean ± SD	*P* Value	Mean ± SD	*P* Value	Mean ± SD	*P* Value	Mean ± SD	*P* Value	Mean ± SD	*P* Value
UDVA (logMAR)	0.66 ± 0.26	0.39 ± 0.21	<.001	0.44 ± 0.19	.001	0.58 ± 0.21	.142	0.58 ± 0.20	.153	0.62 ± 0.17	.250
UDVA (logMAR)	0.33 ± 0.18	0.18 ± 0.10	.001	0.25 ± 0.13	.033	0.29 ± 0.13	.162	0.29 ± 0.16	.171	0.31 ± 0.18	.375
MRSE (D)	−4.39 ± 1.46	−0.70 ± 1.14	<.001	−2.91 ± 1.17	<.001	−3.91 ± 1.32	<.001	−4.28 ± 1.44	.102	−4.38 ± 1.43	.806
Cylinder (D)	−3.60 ± 1.21	−1.22 ± 0.54	<.001	−2.98 ± 0.92	<.001	−3.38 ± 1.03	.001	−3.53 ± 1.12	.129	−3.58 ± 1.19	.426

CDVA = corrected distance visual acuity; MRSE = manifest refraction spherical equivalent; UDVA = uncorrected distance visual acuity

6 months. No eye lost lines of CDVA or UDVA from baseline at the end of 12 months.

Table 1 also shows the changes in the mean manifest refraction spherical equivalent (MRSE) and cylindrical values over time. Improvement in the mean preoperative MRSE was statistically significant 1 month, 3 months, and 6 months postoperatively (all $P < .001$). However, the improvement was lost after 6 months ($P = .102$ at 9 months; $P = .806$ 12 months). The cylindrical values paralleled the change in the MRSE, with a statistically significant reduction in cylinder through 6 months and a return to baseline thereafter.

The mean K value was 49.1 ± 2.43 D preoperatively, 43.50 ± 3.04 D 1 month postoperatively ($P < .001$), 45.7 ± 3.25 D at 3 months ($P < .001$), 47.5 ± 2.99 D at 6 months ($P < .001$), 48.2 ± 3.02 D at 9 months ($P = .014$), and 48.4 ± 3.00 D at 12 months ($P = .015$). Although the eyes remained significantly flattened than preoperatively, the effective therapeutic change started to regress after 1 month. Figure 2 shows the change in and distribution of the K values over time.

The mean endothelial cell density was 2610 ± 283 cells/mm^2 preoperatively and 2595 ± 297 cells/mm^2 12 months postoperatively; the difference was not significant ($P = .832$). The degree of pleomorphism and polymegathism remained unchanged throughout the follow-up.

Figure 3 shows a typical refractive power image from a Scheimpflug system. Characteristic central flattening can be seen.

DISCUSSION

This study evaluated the outcomes of a 2-stage procedure combining microwave thermokeratoplasty and accelerated corneal CXL for the improvement of visual function and stabilization of corneal curvature in patients with keratoconus. The combination procedure was safe, with no loss of visual acuity in any eye from pretreatment to 12 months postoperatively and no endothelial damage in any case.

Microwave thermokeratoplasty was highly effective in the short term, resulting in significant corneal flattening and visual improvement 1 month postoperatively. However, despite the use of immediate postoperative corneal CXL, the effects of thermokeratoplasty on refractive error and the corneal curvature effect regressed significantly after the early

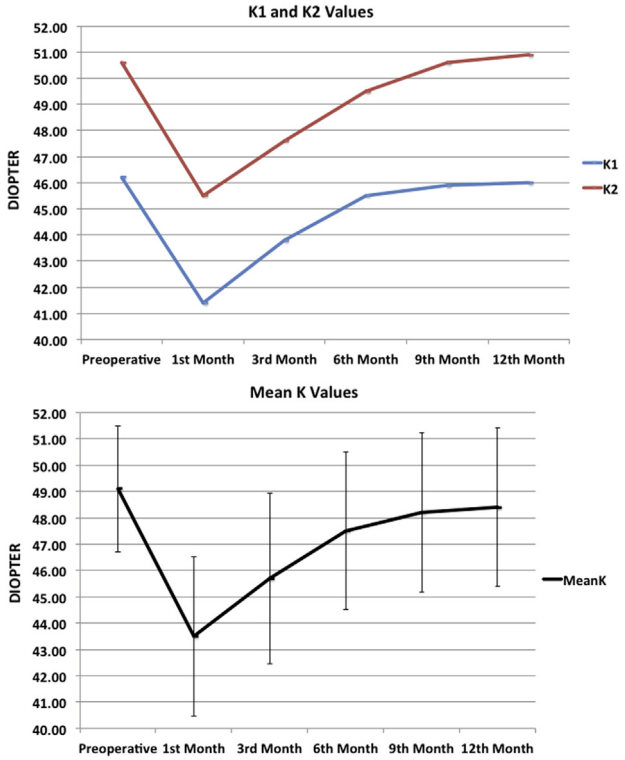

Figure 2. Change in and distribution of K values (K = keratometry).

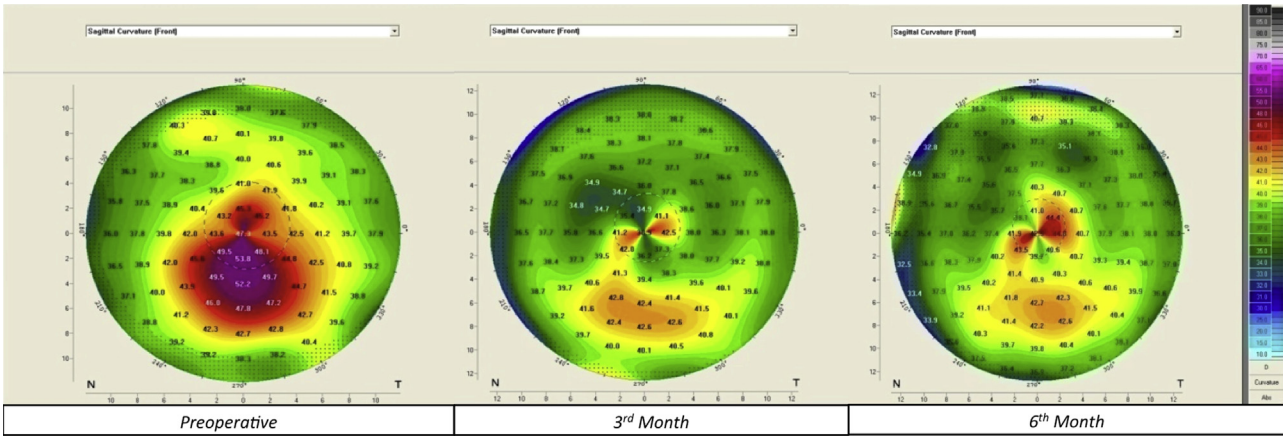

Figure 3. Preoperative and 3- and 6-month postoperative topography map images.

postoperative period, approaching baseline values by 12 months.

We previously reported the results of microwave thermokeratoplasty as a single procedure for treatment of myopic refractive error.[6] The results in the previous study showed a similar evolution after treatment; that is, an initial refractive change, strongly present at 1 month, with subsequent regression to baseline refractive and K values over time. However, although regression occurred in both studies, the return to baseline was slower in the present study. Six months postoperatively, the mean K value and refractive error still showed significant improvement over baseline values. In the previous study of myopic eyes treated with thermokeratoplasty alone, the vision and keratometry regressed to baseline values by 3 months postoperatively. Besides the addition of CXL, the 2 studies also differed in baseline corneal biomechanical properties; that is, myopia with no pathology versus a diseased state. Therefore, the slower return to baseline corneal curvature could be a consequence of a greater initial treatment effect, differences in the biomechanical behavior of the cornea, or a stabilizing effect induced by the addition of CXL.

From a scientific perspective, the next logical step would be to study the effect of thermokeratoplasty alone in eyes with keratoconus to better understand whether the CXL portion of the procedure affects the rate of treatment regression. Although such a study design might provide valuable information on whether there is the potential to improve the stabilization by optimizing CXL treatment parameters, ethical considerations limit the feasibility of withholding the treatment from patients with progressive keratoconus. Although the treatment effect of thermokeratoplasty was lost over the 1-year period, the K values at 12 months remained equivalent to or slightly better than baseline findings. Although it is impossible to separate the response to thermokeratoplasty from the response to accelerated CXL in this study, the results suggest that the combination procedure was effective at delaying progression. However, our previous study[6] showed complete regression of K values; it is likely that the CXL alone had the greatest stabilizing effect in this combination procedure.

We found microwave thermokeratoplasty to be a safe procedure with the potential to significantly improve visual function in patients with keratoconus. Unfortunately, without prevention of early regression of the treatment effect, its usefulness is limited in patients with keratoconus. Recently, advancements in the field of corneal CXL have led to alternative treatment protocols, including the introduction of an ultraviolet-A (UVA) delivery device (KXL II, Avedro, Inc.) with which custom UVA energy distribution patterns can be overlaid on patient topography maps to apply zone-specific UVA treatment. In addition, recent laboratory studies[11] used Brillouin scattering microscopy to measure regional changes in corneal biomechanical properties after CXL. Access to clinical tools incorporating this technology (in development) might provide an improved understanding of the temporal response to thermokeratoplasty and CXL and has the potential to drive further study of alternative methods of improving the stability of the corneal response to microwave thermokeratoplasty. Potential alternative methods include specific crosslinking UVA-energy distribution patterns, application of a greater total UVA energy dose, or staging the procedures with a longer time (hours or days) between the microwave thermokeratoplasty treatment and the subsequent corneal CXL treatment or high-UV irradiance.

WHAT WAS KNOWN

- All ablation procedures depend on removal of tissue and thus change the biomechanical properties of the cornea.

WHAT THIS PAPER ADDS

- Combined microwave thermokeratoplasty and accelerated CXL for keratoconus might have the potential to decrease the number of corneal transplantations performed in patients who have no other treatment alternative.
- Although there was a significant change in refraction after treatment, the changes were temporary, regressing over the 12-month follow-up.

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