Effect of Timolol on Refractive Outcomes in Eyes With Myopic Regression After Laser In Situ Keratomileusis: A Prospective Randomized Clinical Trial

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• PURPOSE: **To compare the effects of timolol on refractive outcomes in eyes with myopic regression after laser in situ keratomileusis (LASIK) with a control-matched group.**

• DESIGN: **Prospective, randomized, parallel-controlled, double-masked clinical trial. A computer-generated randomization list based on random block permutation (length 4 to 8) was used for treatment allocation.**

• METHODS: SETTING: **Basir Eye Center, Tehran, Iran.** PATIENT POPULATION: **Of 124 eyes with myopic regression after LASIK using Technolas 217-Z, 45 eyes in each group were analyzed.** INTERVENTION: **Patients were randomly assigned into either Group 1, who received timolol 0.5% eye drops, or Group 2, who received artificial tears for 6 months.** MAIN OUTCOME MEASURE: **Spherical equivalent (SE) at 6 months posttreatment.**

• RESULTS: **In Group 1, SE improved from −1.48 ± 0.99 diopter (D) before treatment to −0.88 ± 0.91 D and −0.86 ± 0.93 D 6 months after treatment and 6 months after timolol discontinuation, respectively ($P < .001$). In Group 2, it was −1.57 ± 0.67 D, −1.83 ± 0.76 D, and −1.91 ± 0.70 D, respectively ($P < .001$). SE was significantly better in Group 1 6 months after treatment and 6 months after discontinuation of treatment ($P < .001$ for both comparisons). There was a 0.26 D decrease in SE improvement every 4 months after the surgery in the Group 1 ($P < .001$).**

• CONCLUSIONS: **Timolol application is effective for the treatment of myopic regression after LASIK compared with control group. Its effects last for at least 6 months after its discontinuation.** **(Am J Ophthalmol 2012; 154:790–798. © 2012 by Elsevier Inc. All rights reserved.)**

DESPITE THE IMPROVEMENTS IN THE NOMOGRAMS, ablation parameters, and advances in excimer laser technology, up to 28% of refractive surgery patients still continue to experience myopic regression.[1–4]

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In previous studies, "regression" was defined as a 0.25 diopter (D) or greater myopic shift occurring between follow-up visits.[1,2,5,6] The main possible explanations for regression are focused on the increases in corneal thickness and the postoperative forward shift of the cornea.[2,7–10]

In the forward shift theory, thinner cornea, higher intraocular pressure, and higher myopia requiring greater laser ablation have been reported to increase the risk of myopic regression.[7,9–15] It has been suggested that intraocular pressure (IOP)-lowering agents can decrease or even improve myopic regression after laser in situ keratomileusis (LASIK).[11,12,16] However, in previous studies, the findings were not compared with a control-matched group. Moreover, it is still not clear what happens to the refractive error when the drops are stopped and whether the refractive error returns to the baseline after the discontinuation of medication. In this prospective, randomized, double-masked, parallel-group, placebo-controlled clinical trial, we compare the effects of timolol vs placebo for the treatment of myopic regression after LASIK; and afterwards, we evaluate what may come about 6 months after the discontinuation of treatment.

MATERIALS AND METHODS

• STUDY DESIGN AND SETTING: This prospective, randomized, placebo-controlled, parallel-group, double-masked clinical trial was performed at Basir Eye Center between March 2009 and January 2011.

• PARTICIPANTS: In this study, patients with myopic regression who were at least 20 years old with the cylinder ≤−1.00 D, preoperative corneal thickness of at least 500 μm, and a postoperative residual stromal bed thickness of more than 250 μm were included. Myopia regression was defined as a 0.25 D or greater myopic shift between the follow-up visits after month 1 postoperatively. Undercorrection is defined as failure to achieve within 1.00 D or greater of the intended correction by 1 week postoperatively; patients meeting this criterion were excluded from the study. Patients with a history of refractive surgery retreatment, previous ocular surgery other than previous LASIK, keratoconus or any ectatic corneal disorder, kera-

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toconus suspect by topography, preoperative corneal opacity, any corneal dystrophies, presence of pterygium, retinal disorders, collagen vascular disorders, diabetes mellitus, glaucoma, cataract, pregnancy, breastfeeding, and systemic corticosteroid therapy were excluded. In order to obviate inter-eye correlation, only 1 eye of a patient was included, in the case that both eyes of a patient had myopic regression.

• **SURGICAL TECHNIQUE:** All patients underwent LASIK using Technolas 217-Z (Bausch and Lomb, Rochester, New York, USA) using the standard method. Lamellar keratotomy had been performed using the M2 microkeratome (Moria, Antony, France) to create an intended 160-μm flap thickness with a superior hinge. The optical zone was 5.5 to 6.0 mm based on the corneal thickness and curvature. In all eyes, attempted correction was aimed at emmetropia. All surgical procedures were performed by 1 of the authors (A.S.). Patients were examined on postoperative days 1, 3, 7, 14, and 28, and then on a monthly basis for a year, and once every 3 months thereafter until 2 years.

• **INTERVENTION:** Patients were randomly assigned into 2 groups. Group 1 included the patients with myopic regression who received timolol 0.5% eye drops twice a day for 6 months; Group 2 included matched controls who received artificial tears in the same manner as did Group 1.

• **OUTCOME MEASURES:** The main outcome measure was the mean spherical equivalent (SE) 6 months after treatment. Secondary outcome measures were the change in visual acuity and the central corneal thickness (CCT) 6 months after treatment.

• **FOLLOW-UP EXAMINATIONSS:** Included patients had a complete eye examination including refraction, uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), slit-lamp biomicroscopy, IOP measurement, corneal pachymetry (UP-800 ultrasound-4, NIDEK Inc, Gamagori, Japan), and dilated funduscopy in different follow-up visits. It has been shown that LASIK for myopia produces underestimation of IOP measured by Goldmann applanation tonometry.[17] PASCAL dynamic contour tonometer (Ziemer Ophthalmic Systems AG, Port, Switzerland) was used for IOP measurement to obviate the effect of corneal morphologic changes after refractive surgery.[18–20] Follow-up visits were scheduled for 3 and 6 months after the treatment. Patients were called for another follow-up visit 6 months after discontinuation of the treatment. Follow-up examinations consisted of slit-lamp microscopy, refraction, UDVA, CDVA, IOP measurement, corneal pachymetry, and dilated funduscopy. All measurements were carried out by 1 optometrist, who was masked to the randomization list, with the same devices throughout the study.

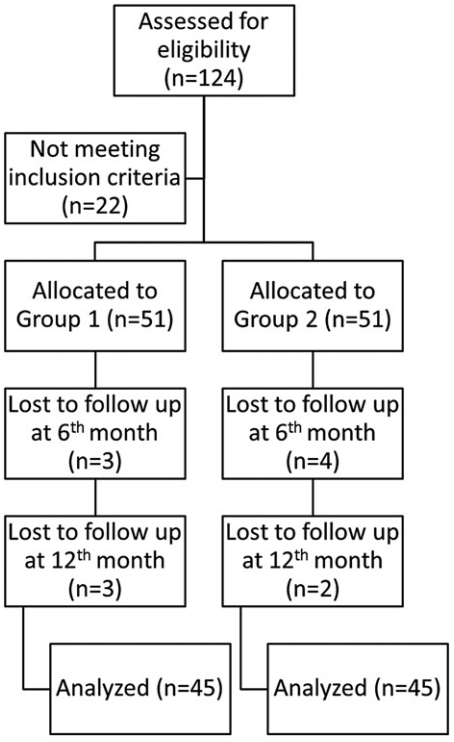

FIGURE 1. Flow diagram shows progression of patients with myopic regression after laser in situ keratomileusis (LASIK) through trial at 6 months after the treatment and at 6 months after discontinuation of the treatment.

• **RANDOMIZATION:** Randomization was performed using the random block permutation method according to a computer-generated randomization list. The block length varied randomly (4 to 6). Random allocation sequence was performed by a biostatistician. The investigators in the study were not informed of the details of the series.

• **MASKING:** Labels of both medication bottles were designed similarly with the same color and shape for masking. A number and a letter indicating in which eye the drop should be administered were stated on the labels. All bottles were prepared and dispensed by a drug store near the clinic based on an instruction given to them by 1 of the authors (Y.V.), who had access to the randomization list and was also responsible for data entry. All eligible patients were referred to the assigned drug store with a letter in hand showing that they were included in this study and in which eye the drop should be administered. The pharmacist gave them appropriate bottles according to the instruction and randomization list.

• **SAMPLE SIZE:** To have a 90% power for detection of 0.5 D difference in the mean SE between the groups as significant (at the 2-sided 5% level) with an assumed standard deviation of 0.48, considering 20% loss to follow-up, 51 eyes for each group were required.

TABLE 1. Demographic Baseline Characteristics (Mean ± SD [Range]) of the Patients With Myopic Regression After Laser In Situ Keratomileusis in 2 Treatment Groups

Baseline Variable	Timolol	Placebo	*P* Value
Age (year)	33.31 ± 10.90 (20.00 to 55.00)	32.42 ± 8.57 (21.00 to 58.00)	.692[a]
Male/female	9/36	15/30	.153[b]
Regression (diopter)	−1.48 ± 1.00 (−4.75 to −0.50)	−1.57 ± 0.67 (−3.00 to −0.50)	.610[c]
CCT (μm)	464.89 ± 45.34 (391.00 to 589.00)	466.84 ± 34.59 (410.00 to 533.00)	.819[c]
IOP (mm-Hg)	12.73 ± 1.43 (9.00 to 15.00)	12.38 ± 1.65 (10.00 to 15.00)	.279[c]
UDVA (logMAR)	−0.29 ± 0.22 (−0.70 to 0.00)	−0.28 ± 0.19 (−0.70 to −0.10)	.883[c]
CDVA (logMAR)	−0.05 ± 0.06 (−0.30 to 0.00)	−0.06 ± 0.08 (−0.30 to 0.08)	.331[a]

CCT = central corneal thickness; CDVA = corrected distance visual acuity; IOP = intraocular pressure; logMAR = logarithm of the minimal angle of resolution; UDVA = uncorrected distance visual acuity.

[a]Mann-Whitney test.

[b]χ^2 test.

[c]Independent-samples *t* test.

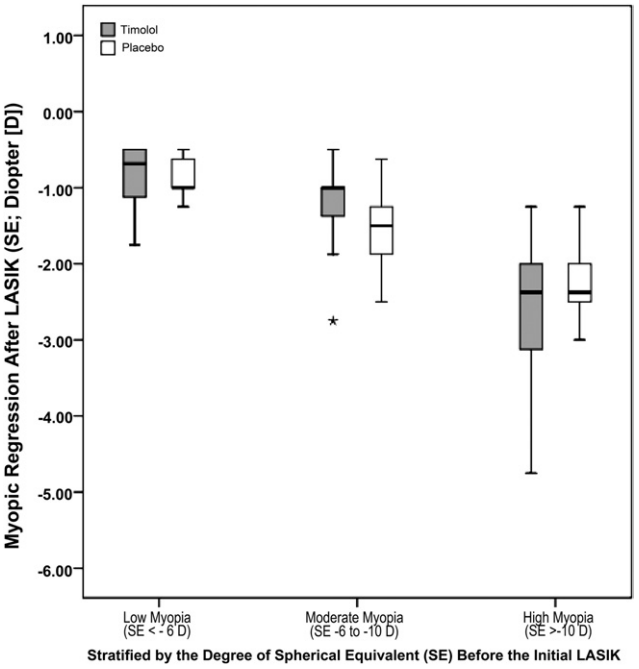

FIGURE 2. Box plot shows there are fairly even distribution of eyes with myopic regression after laser in situ keratomileusis (LASIK) between 2 cohort groups stratified by the degree of spherical equivalent before the initial LASIK ($P = .818$, χ^2 test).

• **STATISTICAL METHODS:** Data were analyzed using SPSS version 17 statistical software (SPSS Inc, Chicago, Illinois, USA). In order to test the normality of the data, we used the Kolmogorov-Smirnov test. To compare the values within groups in different times, we used repeated-measures analysis of variance (ANOVA) test. We used Bonferroni method to adjust multiple comparisons. To compare the results between 2 groups, we used independent-samples t test or Mann-Whitney U test based on normality test results. To obviate the effect of preoperative refraction, attempted correction, degree of myopic regression after LASIK, and the time interval between LASIK and myopic regression as well as their 2 × 2 interactions (effect modification) on the SE and UDVA in each follow-up, we used analysis of covariance. We used repeated-measures ANOVA to evaluate any interaction between 2 groups in terms of trend of changes. To evaluate the influence of preoperative degree of myopia, all eyes were stratified into 3 groups: "low myopia," with preoperative SE below −6.0 D; "moderate myopia," with preoperative SE from −6.0 D to less than −10 D; and "high myopia," with preoperative SE greater than or equal to −10 D. *P* value less than .05 was considered significant.

RESULTS

IN THIS TRIAL, 124 EYES OF 124 PATIENTS WERE ENROLLED and assessed for eligibility. Of them, 22 eyes did not meet inclusion criteria and were excluded from the study. A total of 102 eyes were randomly assigned into either Group 1 (51 eyes) or Group 2 (51 eyes). Of them, 49 eyes (96.07%) and 48 eyes (94.11%) in Group 1 and 50 eyes (98.03%) and 47 eyes (92.15%) in Group 2 attended follow-up visits 3 and 6 months after surgery, respectively. Finally, 45 eyes (88.23%) in Group 1 and 45 eyes (88.23%) in Group 2 attended the last follow-up and were ultimately analyzed (Figure 1). Both groups were matched in terms of baseline characteristics (Table 1).

Mean time interval between surgery and inclusion into study was 5.03 ± 3.46 months (1−15 months). The SE was −8.10 ± 3.41 D (−14.00 to −2.75 D) in Group 1 and −8.20 ± 3.25 D (−14.50 to −2.88 D) in Group 2 before LASIK ($P = .89$, independent samples *t* test) (Figure 2 and Table 2). Mean myopic regression (SE) was −1.48 ± 0.99 D (−4.75 to −0.50) and −1.57 ± 0.67 D (−3.00 to

TABLE 2. Comparison of Spherical Equivalent in Patients With Myopic Regression After Laser In Situ Keratomileusis in 2 Treatment Groups Stratified by the Degree of Myopia Before the Initial Laser In Situ Keratomileusis

Preoperative Stratification	Treatment Group	N	Postoperative Myopic Regression (SE; Diopter)				95% CI for Difference	*P* Value[a]
			Mean	SD	Minimum	Maximum		
Low myopia (SE <−6 D)	Timolol	16	−.85	.43	−1.75	−.50	−0.03 (−0.31 to 0.24)	.80
	Placebo	12	−.88	.26	−1.25	−.50		
Moderate myopia (SE −6 D to −10 D)	Timolol	16	−1.19	.57	−2.75	−.50	−0.29 (−0.66 to 0.06)	.10
	Placebo	19	−1.49	.45	−2.50	−.63		
High myopia (SE >−10 D)	Timolol	13	−2.61	.96	−4.75	−1.25	0.33 (−0.27 to 0.95)	.26
	Placebo	14	−2.28	.44	−3.00	−1.25		

CI = confidence interval; D = diopter; N = number of cases; SE = spherical equivalent.
[a]Mann-Whitney *U*.

TABLE 3. Comparison of Spherical Equivalent Refraction in Patients With Myopic Regression After Laser In Situ Keratomileusis in 2 Treatment Groups in Different Follow-up Visits

Time (mo)	Treatment Group	Spherical Equivalent (Diopter)	Difference			*P* Value[a] (Intergroup Comparison)	Adjusted *P* Value[b] (Intergroup Comparison)	*P* Value[c] (Intragroup Comparison)
			Mean	95% Confidence Interval				
				Lower	Upper			
Before treatment	Timolol	−1.48 ± 0.99	−0.91	−0.44	2.26	.61	—	—
	Placebo	1.57 ± 0.67						—
3	Timolol	−1.12 ± 0.99	−0.51	−0.86	−0.16	.004	.012	<.001
	Placebo	−1.63 ± 0.61						>.999
6	Timolol	−0.88 ± 0.91	−0.94	−1.29	−0.59	<.001	.001	<.001
	Placebo	−1.83 ± 0.76						<.001
12	Timolol	−0.86 ± 0.93	−1.05	−1.4	−0.7	<.001	<.001	<.001
	Placebo	−1.91 ± 0.70						<.001

[a]Independent-samples *t* test.
[b]Analysis of covariance.
[c]Repeated measures with Bonferroni correction (comparing with before-treatment value in respective group and follow-up visit).

−0.50) before initiation of the treatment in Groups 1 and 2, respectively (Table 1).

In Group 1, the IOP was significantly decreased to 9.69 ± 1.83 mm Hg (7.00−16.00) and 9.33 ± 1.59 mm Hg (7.00−15.00) 3 and 6 months after timolol application ($P < .001$ for both values). It increased to 12.66 ± 1.39 mm Hg (8.00−15.00) 6 months after discontinuation of the timolol, which was not significantly different from its value before treatment ($P > .999$). In Group 2, it was 12.38 ± 1.65 mm Hg (10.00−15.00) before treatment, which did not change significantly throughout the follow-up visits ($P > .999$ for all follow-up visits).

In Group 1, SE improved 3 and 6 months after initiation of timolol compared with the placebo group (Table 3). Six months after the discontinuation of timolol, SE remained stable and was significantly better than its value before the treatment (Figure 3). In Group 2, the mean SE significantly shifted toward myopia even 12 months after beginning of the placebo (Table 3). After the stratification of cases based on the preoperative degree of myopia (SE), there was a statistically significant difference between Groups 1 and 2 in low and moderate myopia in different follow-up visits. This difference, however, was not noticed in the high myopia group (Table 4). This observation should be cautiously interpreted since there is a lower sample size in the high myopia group than in other groups with a borderline *P* value. After the adjustment of the effects of preoperative refraction, attempted correction, degree of myopic regression after LASIK, and the time interval between LASIK and myopic regression as well as their 2 × 2 interactions (effect modification) on the comparison between 2 cohort groups, the effects of treatment were still statistically significant (Table 3). The mean difference of SE at month 6 after treatment with the baseline was 0.59 ± 0.38 D (−0.13 to 1.75) in Group 1, which shows significant improvement compared with −0.25 ± 0.38 D (−1.00 to 0.38) in Group 2 (95% confidence interval [CI]: −0.85 [−1.01 to −0.69], $P < .001$). Evaluation of the interaction between the time and

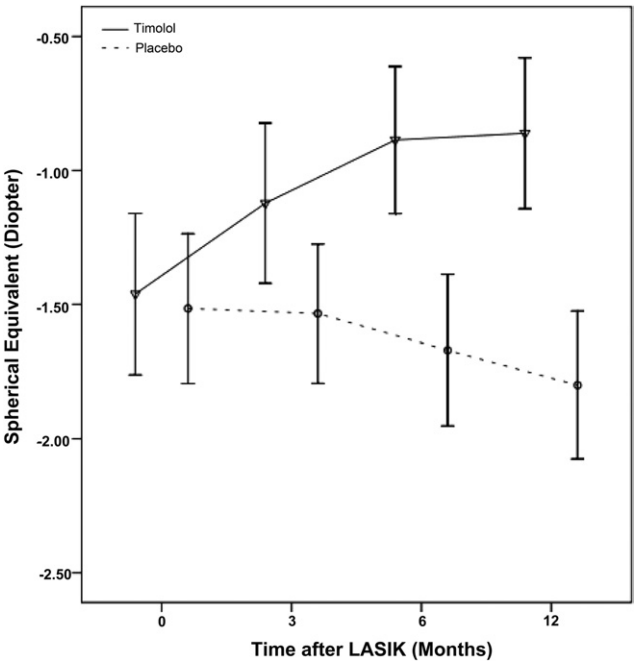

FIGURE 3. Graph demonstrates the mean spherical equivalent (SE) refraction in patients with myopic regression after laser in situ keratomileusis (LASIK) in 2 treatment groups in different follow-up visits. SE improved in patients who received timolol compared to artificial tears 6 months after treatment ($P < .001$; independent samples *t* test). This effect lasted for 6 months after discontinuation of the treatment ($P < .001$; independent samples *t* test). Bar represents 95% confidence interval.

the use of medication showed that there was a statistically significant different trend between 2 groups in terms of SE at months 3 and 6 (adjusted $P < .001$) (Figure 3). Improvement of SE in Group 1 was significantly negatively correlated to the interval between the surgery and the time when patients started to use medication ($P < .001$; $r = -0.6$). This correlation was not observed in the control group ($P = .47$). Using repeated-measures ANOVA, the relation between the amount of SE improvement in different follow-up visits and the time interval between surgery and treatment was evaluated. Interaction between these 2 showed there was a statistically significant difference in the trend of SE in those patients who had an earlier regression who also had been given timolol earlier than those who had a later regression in Group 1 (P for interaction = .001). There was a 0.26 D decrease in SE improvement every 4 months after surgery in Group 1 ($P < .001$; 95% CI: 0.14 to 0.38).

UDVA improved from -0.29 ± 0.22 logMAR before treatment to -0.23 ± 0.21 logMAR ($P = .14$) 3 months and -0.18 ± 0.17 logMAR ($P < .001$) 6 months after the treatment. It remained stable (-0.18 ± 0.17 logMAR) until 6 months after discontinuation of the timolol compared with its value at month 6 ($P > .999$) (Table 5). In Group 2, these values were -0.32 ± 0.21, 0.33 ± 0.19 ($P > .999$), -0.39 ± 0.18 ($P = .03$), and -0.44 ± 0.23 ($P = .01$) logMAR before treatment, 3 and 6 months after placebo use, and 6 months after its discontinuation. Compared with baseline value, there was a mean of -0.08 ± 0.16 logMAR (-0.48 to -0.40) improvement in UDVA in Group 1, whereas it deteriorated with a mean of -0.10 ± 0.14 logMAR (-0.60 to -0.30) in Group 2 ($P < .001$) at the final follow-up (Figure 4).

CDVA improved from -0.05 ± 0.06 logMAR before treatment to -0.043 ± 0.05 ($P = .56$), -0.041 ± 0.06 ($P = .66$), and -0.043 ± 0.05 logMAR ($P = .98$) 3, 6, and 12 months after treatment in Group 1. In Group 2, it was -0.06 ± 0.08 logMAR ($P > .999$), -0.08 ± 0.08 logMAR ($P = .14$), and -0.08 ± 0.08 logMAR ($P = .03$), respectively. CDVA was significantly better in Group 1 at month 6 ($P = .009$, based on Mann-Whitney test) and 12 ($P = .004$, based on Mann-Whitney test) posttreatment compared with Group 2. In Group 1, CCT was 464.89 ± 45.34 μm before treatment, which was not different from Group 2 (466.84 ± 34.59 μm; $P = .143$). At the final follow-up, it was 462.44 ± 43.77 μm and 465.48 ± 33.51 μm in Group 1 and Group 2, respectively ($P > .999$, based on independent samples *t* test). No complications were observed.

DISCUSSION

IN THIS PROSPECTIVE, RANDOMIZED, PLACEBO-CONtrolled, parallel-group, double-masked clinical trial, SE, UDVA, and CDVA improved in patients with myopic regression after timolol application compared with the control group and improvement lasted for at least 6 months after timolol was stopped. There was a significant relation between the amount of SE improvement and the time interval between surgery and treatment. There was also a significant relation in response to the treatment of those patients whose regression started earlier and so who had an earlier start to their treatment in Group 1.

Many factors have been reported to be associated with myopic regression after LASIK, including preoperative refraction,[1,2,21–25] preoperative keratometry,[1,2,21,23,26] corneal thickness,[2,10,25] flap thickness,[27,28] ablation depth,[21] optical zone size,[1,23,29] chronic dry eye,[30] age,[1,22] surgeon,[22] IOP,[21,23] postoperative undercorrection,[1] and humidity.[21] Other factors, such as epithelial hyperplasia, development of new stromal collagen, and nuclear sclerosis of the lens, have also been suggested.[31–36]

In our study, SE improved in Group 1 6 months after IOP-lowering agent application compared with placebo group (0.6 D improvement in Group 1 vs 0.26 D deterioration in Group 2 at month 6). It has been shown that forward shift of the cornea can be one of the factors responsible for regression after refractive surgery.[8,10–14,37] Kamiya and associates[12] conducted a study to assess the effects of nipradilol, an IOP-lowering agent, in eyes with myopic regression after LASIK. This preliminary study

TABLE 4. Comparison of Spherical Equivalent Refraction (Mean ± SD) in Patients With Myopic Regression After Laser In Situ Keratomileusis in 2 Treatment Groups Stratified by the Degree of Myopia Before the Initial Laser In Situ Keratomileusis in Different Follow-up Visits

Preoperative Stratification	Time After Treatment (mo)	Treatment Group	N	SE (D)	Difference			*P* Value[a]
					Mean	95% Confidence Interval		
						Lower	Upper	
Low myopia (SE <−6 D)	3	Timolol	16	−0.53 ± 0.47	−0.48	−0.81	−0.14	.006
		Placebo	12	−1.02 ± 0.38				
	6	Timolol	16	−0.30 ± 0.35	−0.79	−1.08	−0.51	<.001
		Placebo	12	−1.10 ± 0.37				
	12	Timolol	16	−0.28 ± 0.36	−0.96	−1.29	−0.62	<.001
		Placebo	12	−1.25 ± 0.46				
Moderate myopia (SE −6 D to −10 D)	3	Timolol	16	−0.81 ± 0.66	−0.83	−1.23	−0.42	<.001
		Placebo	19	−1.64 ± 0.47				
	6	Timolol	16	−0.55 ± 0.50	−1.23	−1.63	−0.83	<.001
		Placebo	19	−1.78 ± 0.66				
	12	Timolol	16	−0.52 ± 0.52	−1.37	−1.78	−0.97	<.001
		Placebo	19	−1.90 ± 0.64				
High myopia (SE >−10 D)	3	Timolol	13	−2.22 ± 0.95	0.06	−.55	0.68	.826
		Placebo	14	−2.15 ± 0.48				
	6	Timolol	13	−2.00 ± 0.78	−0.49	−1.04	0.04	.069
		Placebo	14	−2.50 ± 0.52				
	12	Timolol	13	−1.98 ± 0.87	−0.53	−1.09	0.02	.058
		Placebo	14	−2.51 ± 0.37				

D = diopter; N = number of cases; SE = spherical equivalent.
[a]Independent-samples *t* test.

TABLE 5. Comparison of Uncorrected Distance Visual Acuity (Mean ± SD) in Patients With Myopic Regression After Laser In Situ Keratomileusis in 2 Treatment Groups in Different Follow-up Visits

Time (mo)	Treatment Groups	UDVA (logMAR)	Difference			*P* Value[a] (Intergroup Comparison)	Adjusted *P* Value[b] (Intergroup Comparison)	*P* Value[c] (Intragroup Comparison)
			Mean	95% Confidence Interval				
				Lower	Upper			
Before treatment	Timolol	−0.29 ± .22	0.009	−0.07	0.09	.883	—	—
	Placebo	−0.28 ± 0.19						—
3	Timolol	−0.25 ± 0.20	−0.05	−0.14	0.02	.186	.078	.007
	Placebo	−0.31 ± 0.19						.27
6	Timolol	−0.20 ± 0.16	−0.16	−0.24	−0.08	<.001	.004	<.001
	Placebo	−0.36 ± 0.20						<.001
12	Timolol	−0.21 ± 0.19	−0.17	−0.26	−0.08	<.001	.041	.011
	Placebo	−0.38 ± 0.22						<.001

logMAR = logarithm of the minimal angle of resolution; UDVA = uncorrected distance visual acuity.
[a]Independent-samples *t* test.
[b]Analysis of covariance.
[c]Repeated measures with Bonferroni correction (comparing with before-treatment value in respective group and follow-up visit).

without control group showed nipradilol was effective for the reduction of the refractive regression. They finally suggested that backward movement of the cornea may be responsible for myopic regression after LASIK.[12] It was suggested that the greater forward shift of the cornea occurs in eyes with less corneal thickness, higher IOP, and more laser ablation.[9,12] There is a debate regarding the role of CCT in myopic regression. In a study by Chayet and associates,[2] without the control of nonregressive eyes, a progressive increase in CCT was observed in the eyes with refractive regression after LASIK. It has been suggested that it is the stromal wound healing and remodeling that

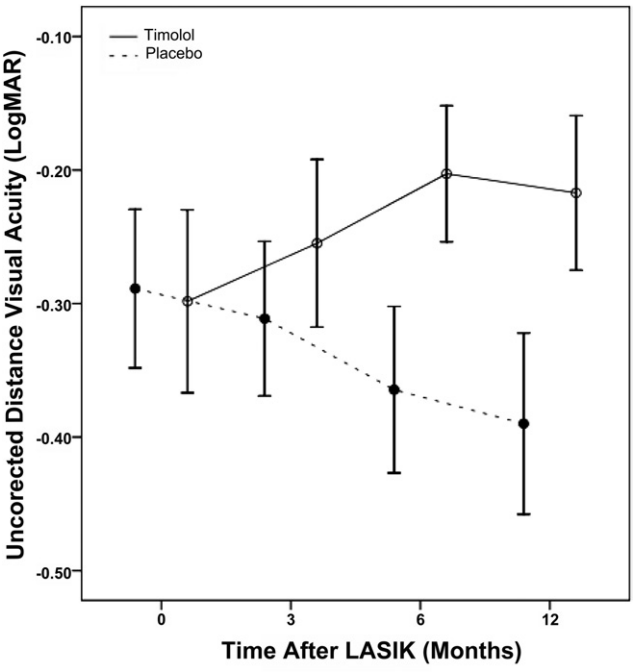

FIGURE 4. Graph demonstrates the mean uncorrected distance visual acuity (logMAR) in patients with myopic regression after laser in situ keratomileusis (LASIK) in 2 treatment groups in different follow-up visits. Uncorrected distance visual acuity improved in patients who received timolol compared to artificial tears 6 months after treatment ($P < .001$; independent samples *t* test). This effect lasted for 6 months after discontinuation of the treatment ($P < .001$; independent samples *t* test). Bar represents 95% confidence interval.

gradually lead to stromal thickening.[10,17,36,38] Stromal thickening after LASIK could be considered as a presentation of the process of corneal repair following keratotomy. In turn, some studies have attributed regression after LASIK to epithelial hyperplasia and stromal remodeling.[39,40] Pan and associates[10] compared regressive eyes with nonregressive eyes after LASIK and indicated that refractive regression after LASIK might be mainly induced by corneal protrusion rather than by central corneal thickening. Although there was an improvement in refraction and visual acuity in Group 1 compared with the control group, we did not find any difference in terms of the CCT between 2 groups in different follow-up visits. These results are consistent with Gullatrand's principle that the change of corneal thickness plays a subtle role in the total refraction of an eye, even in corneal refraction.

It has been reported that the myopic regression after LASIK starts within the first postoperative week, peaks within 6 months, and may last even 1 to 2 years after surgery.[1,2,21,23,41–45] In our study, there was a significant relation between the amount of SE improvement and the time interval between surgery and the beginning of the treatment. In other words, patients who developed myopic regression closer to the time of surgery, whose treatment had started earlier, had a better prognosis with this type of treatment. This can be explained by the biomechanical changes after refractive surgery. The biomechanical strength of the cornea can be substantially weakened by stromal tissue reduction during the early period after LASIK. It has been shown that anterior corneal stroma has the greatest cohesive tensile strength.[17,46] This is because the load-bearing function of the anterior stroma is disabled after keratotomy; only the weaker deep stroma is left to maintain corneal integrity.[47] This loss of load-bearing tissue would compound any innate mechanical weakness of the cornea, which is then exacerbated by LASIK.[48] The cornea begins to remodel stroma after LASIK and it takes time to regain its stability.[49] Given that the posterior cornea is the first barrier to resist the IOP, anterior bowing of the posterior cornea may be expected. The counteracting corneal bowing factor might be caused by corneal tensile strength, which would increase progressively by mechanisms in which keratocytes or their derivatives "sense" local changes in strain and then respond with an appropriate (or, in the case of progressive regression, inappropriate) series of actions for remodeling such areas to reduce or redistribute the mechanical stimulus.[17] When the corneal biomechanical strength has sufficiently recovered to overcome the strength of IOP, the bowing of the posterior cornea could stop or even reverse.[8,50–53] This may explain why regressive eyes closer to the surgery are more responsive to an IOP-lowering agent. In our study, there was a 0.26 D decrease in SE improvement every 4 months from the time of the surgery.

In the study by Kamiya and associates[12] the question of what happens to the refractive error when the drops are stopped[54] remained to be clarified. Hiatt and associates[11] continued to use topical application of IOP-lowering agent for 7 months, but the recurrence occurred on topography at 10 months after treatment. In contrast, in another study corneal ectasia did not recur on topography after the normalization of IOP during a 12-month follow-up.[37] In our study, however, we kept our patients under treatment for only 6 months and were not successful in asking them to continue the use of drops longer than that. It was both time-consuming and difficult to explain to them the advantages of such noninvasive treatment over a high-risk, yet more effective, surgical enhancement. We called our patients to come for another follow-up visits 6 months after the discontinuation of the treatment. Interestingly, 6 months after the treatment, SE did not return to the baseline and was still significantly better in comparison to the control group. Whether this improvement is just for 6 months or it maintains for a longer period needs longer follow-up.

We had some limitations in this study. Topical therapy is not without potential side effects. Although we cannot refute the possibility that the long-term use of any kinds of eye drops may affect corneal epithelium or tear film function, it was observed that timolol and artificial tears

did not induce a significant change or complications in the ocular surface of our patients. In addition, a study evaluating the safety of this type of treatment seems mandatory. Another clinical trial with control-matched postsurgical patients without myopic regression and with the evaluation of the keratometric changes as well as the posterior corneal forward shift in 2 parallel groups can strengthen our evidence regarding its etiology, and the safety and efficacy of antiglaucoma therapy for patients with myopic regression.

Based on our results, timolol application is effective for the correction of the refractive regression compared with control group after LASIK. Its effects last for at least 6 months after timolol discontinuation. Although the refractive effect of this treatment is mild (mean difference of 0.62 D at month 12), it should be tried soon after the surgeon observes any signs of regression, as patients who develop myopic regression closer to the time of surgery are more responsive to this type of treatment.

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REFERENCES

1. Chen YI, Chien KL, Wang IJ, et al. An interval-censored model for predicting myopic regression after laser in situ keratomileusis. *Invest Ophthalmol Vis Sci* 2007;48(8):3516–3523.
2. Chayet AS, Assil KK, Montes M, Espinosa-Lagana M, Castellanos A, Tsioulias G. Regression and its mechanisms after laser in situ keratomileusis in moderate and high myopia. *Ophthalmology* 1998;105(7):1194–1199.
3. Yuen LH, Chan WK, Koh J, Mehta JS, Tan DT. A 10-year prospective audit of LASIK outcomes for myopia in 37,932 eyes at a single institution in Asia. *Ophthalmology* 2010;117(6):1236–1244.e1.
4. Zalentein WN, Tervo TM, Holopainen JM. Seven-year follow-up of LASIK for myopia. *J Refract Surg* 2009;25(3):312–318.
5. Melki SA, Azar DT. LASIK complications: etiology, management, and prevention. *Surv Ophthalmol* 2001;46(2):95–116.
6. Sridhar MS, Rao SK, Vajpayee RB, Aasuri MK, Hannush S, Sinha R. Complications of laser-in-situ-keratomileusis. *Indian J Ophthalmol* 2002;50(4):265–282.
7. Kamiya K, Miyata K, Tokunaga T, Kiuchi T, Hiraoka T, Oshika T. Structural analysis of the cornea using scanning-slit corneal topography in eyes undergoing excimer laser refractive surgery. *Cornea* 2004;23(8 Suppl):S59–64.
8. Qi H, Hao Y, Xia Y, Chen Y. Regression-related factors before and after laser in situ keratomileusis. *Ophthalmologica* 2006;220(4):272–276.
9. Baek T, Lee K, Kagaya F, Tomidokoro A, Amano S, Oshika T. Factors affecting the forward shift of posterior corneal surface after laser in situ keratomileusis. *Ophthalmology* 2001;108(2):317–320.
10. Pan Q, Gu YS, Wang J, et al. Differences between regressive eyes and non-regressive eyes after LASIK for myopia in the time course of corneal changes assessed with the Orbscan. *Ophthalmologica* 2004;218(2):96–101.
11. Hiatt JA, Wachler BS, Grant C. Reversal of laser in situ keratomileusis-induced ectasia with intraocular pressure reduction. *J Cataract Refract Surg* 2005;31(8):1652–1655.
12. Kamiya K, Aizawa D, Igarashi A, Komatsu M, Shimizu K. Effects of antiglaucoma drugs on refractive outcomes in eyes with myopic regression after laser in situ keratomileusis. *Am J Ophthalmol* 2008;145(2):233–238.
13. Kamiya K, Oshika T. Corneal forward shift after excimer laser keratorefractive surgery. *Semin Ophthalmol* 2003;18(1):17–22.
14. Miyata K, Kamiya K, Takahashi T, et al. Time course of changes in corneal forward shift after excimer laser photorefractive keratectomy. *Arch Ophthalmol* 2002;120(7):896–900.
15. Miyata K, Tokunaga T, Nakahara M, et al. Residual bed thickness and corneal forward shift after laser in situ keratomileusis. *J Cataract Refract Surg* 2004;30(5):1067–1072.
16. El-Awady HE, Ghanem AA, Gad MA. Evaluation of the role of timolol 0.1% gel in myopic regression after laser in situ keratomileusis. *Saudi J Ophthalmol* 2010;24:81–86.
17. Dupps WJ Jr, Wilson SE. Biomechanics and wound healing in the cornea. *Exp Eye Res* 2006;83(4):709–720.
18. Kniestedt C, Kanngiesser H, Stamper RL. Assessment of Pascal dynamic contour tonometer in monitoring IOP after LASIK. *J Cataract Refract Surg* 2005;31(3):458–459.
19. Martinez-de-la-Casa JM, Garcia-Feijoo J, Vico E, et al. Effect of corneal thickness on dynamic contour, rebound, and Goldmann tonometry. *Ophthalmology* 2006;113(12):2156–62.
20. Qazi MA, Sanderson JP, Mahmoud AM, Yoon EY, Roberts CJ, Pepose JS. Postoperative changes in intraocular pressure and corneal biomechanical metrics: Laser in situ keratomileusis versus laser-assisted subepithelial keratectomy. *J Cataract Refract Surg* 2009;35(10):1774–1788.

21. Lyle WA, Jin GJ. Retreatment after initial laser in situ keratomileusis. *J Cataract Refract Surg* 2000;26(5):650–659.
22. Hu DJ, Feder RS, Basti S, et al. Predictive formula for calculating the probability of LASIK enhancement. *J Cataract Refract Surg* 2004;30(2):363–368.
23. Perez-Santonja JJ, Bellot J, Claramonte P, Ismail MM, Alio JL. Laser in situ keratomileusis to correct high myopia. *J Cataract Refract Surg* 1997;23(3):372–385.
24. Pallikaris IG, Siganos DS. Laser in situ keratomileusis to treat myopia: early experience. *J Cataract Refract Surg* 1997;23(1): 39–49.
25. Magallanes R, Shah S, Zadok D, et al. Stability after laser in situ keratomileusis in moderately and extremely myopic eyes. *J Cataract Refract Surg* 2001;27(7):1007–1012.
26. Rao SK, Cheng AC, Fan DS, Leung AT, Lam DS. Effect of preoperative keratometry on refractive outcomes after laser in situ keratomileusis. *J Cataract Refract Surg* 2001;27(2): 297–302.
27. Eleftheriadis H, Prandi B, Diaz-Rato A, Morcillo M, Sabater JB. The effect of flap thickness on the visual and refractive outcome of myopic laser in situ keratomileusis. *Eye (Lond)* 2005;19(12):1290–1296.
28. Wilson SE, Mohan RR, Hong JW, Lee JS, Choi R. The wound healing response after laser in situ keratomileusis and photorefractive keratectomy: elusive control of biological variability and effect on custom laser vision correction. *Arch Ophthalmol* 2001;119(6):889–896.
29. Ditzen K, Handzel A, Pieger S. Laser in situ keratomileusis nomogram development. *J Refract Surg* 1999;15(2 Suppl): S197–201.
30. Albietz JM, Lenton LM, McLennan SG. Chronic dry eye and regression after laser in situ keratomileusis for myopia. *J Cataract Refract Surg* 2004;30(3):675–684.
31. Gauthier CA, Holden BA, Epstein D, Tengroth B, Fagerholm P, Hamberg-Nystrom H. Role of epithelial hyperplasia in regression following photorefractive keratectomy. *Br J Ophthalmol* 1996;80(6):545–548.
32. Gauthier CA, Holden BA, Epstein D, Tengroth B, Fagerholm P, Hamberg-Nystrom H. Factors affecting epithelial hyperplasia after photorefractive keratectomy. *J Cataract Refract Surg* 1997;23(7):1042–1050.
33. Lohmann CP, Reischl U, Marshall J. Regression and epithelial hyperplasia after myopic photorefractive keratectomy in a human cornea. *J Cataract Refract Surg* 1999;25(5):712–715.
34. Moller-Pedersen T, Cavanagh HD, Petroll WM, Jester JV. Stromal wound healing explains refractive instability and haze development after photorefractive keratectomy: a 1-year confocal microscopic study. *Ophthalmology* 2000; 107(7):1235–1245.
35. Moller-Pedersen T, Li HF, Petroll WM, Cavanagh HD, Jester JV. Confocal microscopic characterization of wound repair after photorefractive keratectomy. *Invest Ophthalmol Vis Sci* 1998;39(3):487–501.
36. Park CK, Kim JH. Comparison of wound healing after photorefractive keratectomy and laser in situ keratomileusis in rabbits. *J Cataract Refract Surg* 1999;25(6):842–850.
37. Toshino A, Uno T, Ohashi Y, Maeda N, Oshika T. Transient keratectasia caused by intraocular pressure elevation after laser in situ keratomileusis. *J Cataract Refract Surg* 2005;31(1):202–204.
38. Netto MV, Mohan RR, Ambrosio R Jr, Hutcheon AE, Zieske JD, Wilson SE. Wound healing in the cornea: a review of refractive surgery complications and new prospects for therapy. *Cornea* 2005;24(5):509–522.
39. Reinstein DZ, Silverman RH, Sutton HF, Coleman DJ. Very high-frequency ultrasound corneal analysis identifies anatomic correlates of optical complications of lamellar refractive surgery: anatomic diagnosis in lamellar surgery. *Ophthalmology* 1999; 106(3):474–482.
40. Spadea L, Fasciani R, Necozione S, Balestrazzi E. Role of the corneal epithelium in refractive changes following laser in situ keratomileusis for high myopia. *J Refract Surg* 2000; 16(2):133–139.
41. Patel NP, Clinch TE, Weis JR, Ahn C, Lundergan MK, Heidenreich K. Comparison of visual results in initial and re-treatment laser in situ keratomileusis procedures for myopia and astigmatism. *Am J Ophthalmol* 2000;130(1):1–11.
42. Pallikaris IG, Siganos DS. Excimer laser in situ keratomileusis and photorefractive keratectomy for correction of high myopia. *J Refract Corneal Surg* 1994;10(5):498–510.
43. Zaldivar R, Davidorf JM, Shultz MC, Oscherow S. Laser in situ keratomileusis for low myopia and astigmatism with a scanning spot excimer laser. *J Refract Surg* 1997;13(7):614–619.
44. Alio JL, Muftuoglu O, Ortiz D, et al. Ten-year follow-up of laser in situ keratomileusis for myopia of up to −10 diopters. *Am J Ophthalmol* 2008;145(1):46–54.
45. Alio JL, Muftuoglu O, Ortiz D, et al. Ten-year follow-up of laser in situ keratomileusis for high myopia. *Am J Ophthalmol* 2008;145(1):55–64.
46. Randleman JB, Dawson DG, Grossniklaus HE, McCarey BE, Edelhauser HF. Depth-dependent cohesive tensile strength in human donor corneas: implications for refractive surgery. *J Refract Surg* 2008;24(1):S85–89.
47. Dupps WJ Jr, Roberts C. Effect of acute biomechanical changes on corneal curvature after photokeratectomy. *J Refract Surg* 2001;17(6):658–669.
48. Klein SR, Epstein RJ, Randleman JB, Stulting RD. Corneal ectasia after laser in situ keratomileusis in patients without apparent preoperative risk factors. *Cornea* 2006;25(4):388–403.
49. Roy AS, Dupps WJ Jr. Effects of altered corneal stiffness on native and postoperative LASIK corneal biomechanical behavior: A whole-eye finite element analysis. *J Refract Surg* 2009;25(10):875–887.
50. Geggel HS, Talley AR. Delayed onset keratectasia following laser in situ keratomileusis. *J Cataract Refract Surg* 1999; 25(4):582–586.
51. Schmitt-Bernard CF, Lesage C, Arnaud B. Keratectasia induced by laser in situ keratomileusis in keratoconus. *J Refract Surg* 2000;16(3):368–370.
52. Joo CK, Kim TG. Corneal ectasia detected after laser in situ keratomileusis for correction of less than −12 diopters of myopia. *J Cataract Refract Surg* 2000;26(2):292–295.
53. Randleman JB, Russell B, Ward MA, Thompson KP, Stulting RD. Risk factors and prognosis for corneal ectasia after LASIK. *Ophthalmology* 2003;110(2):267–275.
54. Weiss JS, Mokhtarzadeh M. Myopic regression after laser in situ keratomileusis: a medical alternative to surgical enhancement. *Am J Ophthalmol* 2008;145(2):189–190.

Biosketch

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