Effect of timolol maleate (0.5%) in the management of myopic regression post laser-assisted in-situ keratomileusis: Clinical and topographical outcomes

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Purpose: The aim of this study was to analyze the effect of timolol maleate (0.5%) eye drops in the treatment of myopic regression after laser-assisted in-situ keratomileusis (LASIK). Methods: The study was conducted at a tertiary care eye hospital in north India between April 2017 & March 2018 as a prospective interventional study. Patients who underwent uneventful myopic LASIK with Hansatome mechanical keratome and presented with regression were included in the study. Baseline demographic characteristics, time to presentation with regression best-corrected visual acuity (BCVA), refraction, intraocular pressure, central corneal thickness and keratometry were recorded at baseline and at each follow-up visit. The enrolled patients were prescribed timolol maleate (0.5%) eyedrops twice daily. They were followed up every month till 3 months on timolol maleate (0.5%) eyedrops and at 6 months post stopping the treatment. Results: Twenty-nine eyes of 15 patients were enrolled in the study. Mean pre LASIK spherical equivalent (SE) was – 7.48 ± 2.9 Diopters (Range -3.125 to -11.75 Diopters) and mean regression spherical equivalent was –1.02 ± 1.1 Diopters. There was a decrease in mean SE from presentation (intervention start point) up to 6 months follow-up (~1.34 ± 0.89 to –0.30 ± 0.29 Diopters). While posterior corneal curvature (K1 and K2 Back) changed significantly over treatment period (P = 0.0029, P = 0.0024 respectively), changes in anterior corneal curvature (K1 and K2 Front) were not significant (P = 0.05, P = 0.06 respectively). Central corneal thickness (CCT) and intraocular pressure (IOP) did not change significantly over treatment course. Conclusion: Timolol maleate (0.5%) eyedrop is an effective modality for the treatment of refractive regression post LASIK circumventing the need for laser re-treatment in such patients. The most probable mechanism is reversal of the anterior bowing of the cornea in response to intraocular pressure changes.

Key words: Beta blockers, LASIK, regression

Laser-Assisted In-Situ Keratomileusis (LASIK) is now a universal and widely performed procedure for correction of refractive error. Since Jose Barraquer developed the microkeratome and keratomileusis technique in the 1950s, refractive surgery has evolved over six decades.[1] Approximately 40 million procedures have been performed till date since the procedure has been commercially available from early 1990s.[2] With advances in technology such as wavefront-guided techniques, bladeless femtosecond flap techniques, flapless techniques such as Small incision lenticule extraction (SMILE), superior results in terms of visual acuity and quality of vision can now be achieved.[3]

While the procedure is largely standardized with predictable outcomes, attributable to improvisations in ablation parameters, normograms and sophisticated centration and eye tracking systems, 20%–30% patients may still experience “regression”.[4] Regression is defined as the gradual, partial, or total loss of initial correction of refractive error post-refractive surgery.[4,5] Mechanism of myopic regression has largely been attributed to the ‘forward shift theory” in various studies, which ascribes regression to keratectasia under the effect of intraocular pressure (IOP).[6,7] Various factors such as high pre-operative spherical equivalent, thinner corneas, raised postoperative intraocular pressure, under-correction and older age of the patient have been reported to increase the risk of myopic regression.[8,9]

While retreatment with excimer laser is an option, flap lifting can increase the risk of epithelial ingrowth and flap filleting.[10] As IOP is a modifiable factor, it has been suggested that topical IOP lowering agents suggest as timolol maleate, a non-selective β blocker, can improve myopic regression after LASIK without the need for re-surgery.[11-14] We undertook a prospective interventional study, to analyze the effect of timolol maleate (0.5%) eyedrops (TM) in treatment of myopic regression after LASIK and serially followed up the cases on a topographer to study the various possible mechanisms for the same.

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Methods

Study design and setting
This was a prospective interventional study conducted at the department of cornea and refractive surgery services of a tertiary care eye hospital in north India between April 2017 and March 2018. The study was approved by the Institutional Ethics Committee (IEC) and was conducted in adherence to the tenets of the Declaration of Helsinki. Informed written consent for the investigations and medical treatment was taken from all patients.

Participants
Patients who presented with regression after undergoing uneventful myopic LASIK with hansatome mechanical keratome performed by a single surgeon (UM) were included in the study. Regression was defined as uncorrected distance visual acuity (UDVA) of 20/20 at final follow-up post LASIK, but UDVA loss of two lines, which was correctable with residual refraction at month 3 (or beyond) post-operatively. Only those patients who had finished their post-operative course of topical steroids were included in the study.

Patients with history of corneal ectasia, keratoconus, glaucoma, cataract, refractive surgery re-treatment, previous ocular surgery other than LASIK, posterior segment disorders, pregnancy or breastfeeding were excluded from the study.

Treatment and follow-up
Baseline demographic characteristics and time to presentation with regression after undergoing LASIK was noted. UDVA (log Mar) and refractive error were recorded and a baseline topography (Pentacam, Oculus, Wetzlar, Germany) was performed. The IOP was recorded by Goldmann applanation tonometry after topographic evaluation, so as to avoid any error in image capture at all visits. The Goldmann applanation tonometer was calibrated once every month as per standard operating procedure. The enrolled patients were prescribed TM (0.5%) eyedrops twice daily. They were followed up every month till 3 months on TM (0.5%) eyedrops and at 6 months post-treatment. UDVA (log Mar), refraction, IOP measurement, central corneal thickness (CCT) measurement, topography (anterior and posterior keratometry) were performed at every subsequent follow-up. All measurements were carried out by a single optometrist with the same devices throughout the study. Minimum follow-up post completion of treatment was 6 months.

Outcome measures
The primary outcome measure was changed in mean spherical equivalent (SE) at 6 months after completion of treatment. Secondary outcome measures were changed in CCT, IOP and keratometry (anterior and posterior curvatures) respectively at 6 months following completion of treatment.

Statistical analysis
Statistical Package for the Social Sciences software version 23 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Mean and standard deviation was calculated for continuous variables. Categorical variables were reported in percentages. The repeated measure analysis of variance was used to determine the differences between the means of identified parameters at different time points. Mauchly’s Test of sphericity was used to test the assumption of sphericity. If data violated the assumption of sphericity, Greenhouse-Geisser correction was used to test within subject effect. Post hoc tests using the Bonferroni correction was performed. A probability (p) of 0.05 or less was considered statistically significant.

Results
Twenty-nine eyes of 15 patients were enrolled in the study. Male to female ratio in the study was 1:4. Mean age of the patients was 23.55 years (range 21.22-26.56 years). Mean time to presentation with regression from final follow-up (3 months post LASIK) was 24.03 months (range 7.02 – 45.13 months). Mean pre-LASIK refractive error (SE) was – 7.48 ± 2.9 Diopters (range –3.125 to –11.75 Diop ters) and mean regression SE was –1.02 ± 1.1 Diop ters. Mean CCT at presentation was 417.59 ± 75.44 microns while mean pre-intervention IOP was 11.31 ± 1.8 mmHg (range 8-14 mmHg). Mean keratometry values of the anterior and posterior corneal surfaces, measured on topography were 39.86 ± 2.7 Diopters and - 6.52 ± 0.2 Diopters, respectively. We further present in detail, the changes in individual parameters over the course of intervention. A repeated-measures ANOVA with a Greenhouse-Geisser correction was used to determine if changes in various parameters differed statistically significantly between time points. Post hoc tests using the Bonferroni correction were used to discern changes in each parameter.

Spherical equivalent (SE)
The mean SE differed statistically significantly between time points [F (1.432, 40.086) = 17.586, P < 0.0005]. There was a decrease in SE from presentation (intervention start point) to 1 month, 2 months, 3 months, and 6 months follow-up (1.34 ± 0.89 D, -1.03 ± 0.6 D, -0.73 ± 0.45 D, -0.27 ± 0.33 D and 0.30 ± 0.29 D respectively), which was statistically significant (P < 0.0015). There was an increase in SE from 3 months to 6 months follow-up (-0.27 ± 0.33 D and 0.30 ± 0.29 D respectively) after stopping treatment, which was not statistically significantly (P = 1.0) [Fig. 1].

Anterior corneal curvature changes (K1 and K2 front)

K1 front
The mean K1 front differed significantly between different time points [F (2.41, 67.5) = 0.995, P = 0.05]). Mean K1 front did not change significantly from presentation to 1 month follow-up (P = 1.0), 2 months follow-up (P = 1.0), 3 months follow-up (P = 1.0) and 6 months follow-up (P = 1.0). However, there was a statistically significant decrease from 1 month follow-up to 6 months follow-up (P = 0.02) [Fig. 2].

K2 front
The mean K2 front did not differ significantly between different time points [F (1.92, 34.8) = 1.96, P = 0.06)]. Mean K2 front did not change significantly from presentation to 1 month follow-up (P = 1.0), 2 months follow-up (P = 0.45), 3 months follow-up (P = 1.0) and 6 months follow-up (P = 1.0). However, there was a statistically significant increase from 3 months follow-up to 4 months follow-up (P = 0.00) and 5 months follow-up (P = 0.001) [Fig. 2].
Alteration in the corneal curvature as a consequence of the refractive apparatus of the eye is a dynamic system. The Gullstrand principle states that bowing of the posterior corneal surface results in an increase in the negative power while the bowing of the anterior corneal surface results in an increase in the positive refractive power of the eye.\(^5\) Dawson \textit{et al.}\ have reported that anterior one-thirds stroma has a greater cohesive tensile strength than the posterior two-thirds of stroma. This has been attributed to differences in direction of collagen fibrils as well as degree of collagen lamellar interweaving.\(^6\) Post LASIK cornea thus has lesser tensile strength and biomechanical rigidity as a consequence of stromal ablation restricted to the anterior stroma. When such a surface is subjected to effect of IOP, the primary response of the surface is that of “anterior bowing”.

Topical application of the IOP-lowering drug, timolol maleate (0.5\%) was effective in reducing the refractive regression after LASIK in our study. Case reports of transient corneal ectasia and its reversal with IOP reducing drugs has been reported by Hiatt \textit{et al.}\ The use of IOP-lowering agents to treat regression has been reported in studies from across the world such as those by Kamiya \textit{et al.}, Qi \textit{et al.} and Shojaei \textit{et al.}\ On analysis of keratometry findings in our study there were significant changes in the curvature of the posterior surface of the cornea indicating that IOP reduction induced a backward shift and flattening of the cornea with resultant reduction of corneal refractive power.

The natural defence mechanism to counteract anterior bowing has been reported to be stromal remodeling by keratocytes to redistribute the effect of this mechanical strain.\(^{9,20}\) Resultant regression in a post-refractive surgery patient can thus be regarded as a consequence of these two opposing forces, i.e., IOP versus remodeling. Other factors suggested to play a significant role in regression are epithelial hyperplasia and development of new stromal collagen.\(^{21,22}\) Consequently eyes having higher degree of myopia requiring higher ablation, thinner corneas and eyes with higher IOP are expected to be predisposed to develop regression.\(^{23,24}\) It remains however unanswered, as to over what duration of time does this remodeling takes place and to what extent. It has been stated that, the bowing of the posterior cornea arrests once the biomechanical strength of the cornea has been compromised.

Posterior corneal curvature changes (K1 and K2 Back)

\textbf{K1 Back}

The mean K1 back differed significantly between different time points \([F (2.12, 59.47) = 1.96, P = 0.00]\). Mean K1 back changed significantly from presentation to 1 month follow-up \((P = 0.029)\). K1 back did not change significantly from presentation to 2 months follow-up \((P = 1.0)\), 3 months follow-up \((P = 1.0)\) and 6 months follow-up \((P = 0.13)\). However, there was a statistically significant decrease from 1 month to 2 months follow-up \((P = 0.014)\), 3 months follow-up \((P = 0.01)\) and 6 months follow-up \((P = 0.00)\) [Fig. 3].

\textbf{K2 Back}

The mean K2 back differed significantly between different time points \([F (1.73, 48.31) = 13349.1, P = 0.024]\). Mean K2 back did not change significantly from presentation to 1 month follow-up \((P = 1.0)\), 2 months follow-up \((P = 0.29)\), 3 months follow-up \((P = 0.28)\) and 6 months follow-up \((P = 0.36)\). However, there was a statistically significant decrease from 1 month to 2 months follow-up \((P = 0.029)\) and from 2 months to 3 months follow-up \((P = 0.004)\) [Fig. 3].

\textbf{Pachymetry (CCT)}

The mean CCT differed significantly between different time points \([F (1.72, 48.3) = 13349.1, P = 0.024]\). Mean CCT increased significantly from presentation to 3 months follow-up \((P = 0.001)\). Pachymetry did not change significantly from presentation to 1 month follow-up \((P = 0.06)\) and between 3 months follow-up \((P = 1.0)\) and 6 months follow-up \((P = 0.13)\) [Fig. 4].

\textbf{IOP}

The mean IOP differed significantly between different time points \([F (2.23, 62.48) = 13.67, P = 0.002]\). Mean IOP decreased significantly from presentation to 1 month follow-up \((P = 0.007)\), 2 months follow-up \((P = 0.040)\, and 6 months follow-up \((P = 0.012)\). Mean IOP from presentation to 3 months follow-up did not change significantly \((P = 0.66)\). There was significant decrease in mean IOP from 3 months to 6 months follow-up \((P = 0.023)\) [Fig. 5].

\section*{Discussion}

The refractive apparatus of the eye is a dynamic system. Alteration in the corneal curvature as a consequence of the biomechanical changes is known to affect the dioptic power of the eye. The Gullstrand principle states that bowing of the posterior corneal surface results in an increase in the negative power while the bowing of the anterior corneal surface results in an increase in the positive refractive power of the eye.\(^5\) Dawson \textit{et al.}\ have reported that anterior one-thirds stroma has a greater cohesive tensile strength than the posterior two-thirds of stroma. This has been attributed to differences in direction of collagen fibrils as well as degree of collagen lamellar interweaving.\(^3\) Post LASIK cornea thus has lesser tensile strength and biomechanical rigidity as a consequence of stromal ablation restricted to the anterior stroma. When such a surface is subjected to effect of IOP, the primary response of the surface is that of “anterior bowing”.

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\begin{figure}
\centering
\includegraphics[width=\textwidth]{image1}
\caption{Change in mean spherical equivalent (SE) from presentation up to 6 months post treatment with timolol maleate (0.5\%) eyedrop}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image2}
\caption{Change in mean keratometry (anterior corneal curvature) from presentation up to 6 months post treatment with timolol maleate (0.5\%) eyedrop}
\end{figure}
To specifically exclude the established remodeling effects of topical steroids as a confounder, we included only those patients in our study who had completed their course of postoperative topical steroids.

There have been two major dilemmas since IOP lowering agents have been recommended to treat regression. First, does the regression reverse when the eyedrops are stopped? Second, till what time period should one prescribe these agents to prevent regression from recurring. In our study of 6 months follow-up post timolol stoppage, we report no recurrence. However, a controlled study with a longer follow-up and studies based on corneal hysteresis could improve our understanding on the subject better.

Refractive effect of topical IOP lowering agents has been reported to be reversible and mild in previous studies. Also, it has been observed that patients who develop myopic regression closer to the time of surgery are more responsive to this treatment. The mean time to presentation with regression in our study was 24.03 months and mean regression spherical equivalent was $-1.02 \pm 1.1$ Diopters. While the time to reversal with topical therapy may be longer and the amount of reversal that can be corrected lesser as compared to laser re-treatment, it is a less invasive and safer (especially in thinner corneas) alternative to enhancement ablation. Side effects such as ectasia which can be seen post enhancement ablation can also be avoided with this therapy. There are no reported sight-threatening side effects of timolol maleate eyedrops if used in long term. There is always a potential of damage to corneal epithelium and alteration of tear film with long term use of topical medication which must be kept in mind if topical drugs are used to maintain reversal of regression. However, neither we nor previous studies report any ocular surface complications post-treatment.

Various researches have studied modulations in CCT post LASIK and its possible role in subsequent regression. Progressive increase in CCT has been reported by Chayet et al. in eyes presenting with regression. On the contrary, Magallanes et al. reported only a slight increase in CCT in some of their cases and a significant increase in CCT after LASIK in others. We did not find significant changes in corneal thickness before and after treatment in our study.

**Conclusion**

We thus conclude that topical therapy with timolol maleate (0.5%) eyedrops can be used as a treatment modality for treating regression with significant comfort, compliance and safety. All patients presenting with regression do not need laser re-treatment which has its own pitfalls.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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