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Lowering Postoperative Intraocular Pressure Ameliorates Myopic Regression after Laser *in situ* Keratomileusis: A Placebo-Controlled Comparative Study

Tamer Salem and Tarek Nehad

To evaluate the effect of timolol 0.1% gel and latanoprost 0.005% on myopic regression after myopic LASIK surgery in comparison to artificial tears as placebo. The study included 90 patients with mean age of 25.7±5.7 years; 12 patients had bilateral LASIK and both eyes were included in the study. All patients underwent complete ophthalmologic examination for determination of uncorrected and corrected distant visual acuity (UDVA and CDVA), intraocular pressure (IOP), Schrimer test, central corneal pachymetry and corneal topography. These parameters were evaluated at time of inclusion and 3-monthly for 12 months. The percentage of change at the 12th month in comparison to the baseline measures, was calculated for assurance of randomization and accurate evaluation of outcome. Patients were randomly allocated into 3 equal groups: Control group received artificial tears; Timolol group received timolol maleate 0.1% gel once daily and Prostaglandin (PG) group received latanoprost 0.005% eye drops once daily. Topical therapy significantly improved UCDVA and CDVA at the end of follow-up period compared to control group and to their respective baseline measures with significantly higher percentage of improvement in timolol group compared to PG group. Control eyes showed non-significant deterioration of spherical error evaluation and extent of astigmatism at the end of follow-up compared to baseline measures, while both modalities of topical therapy significantly improved it compared to their respective preoperative measures and to control group. Timolol also, significantly improved extent of astigmatism compared to PG. The percentage of increase of corneal thickness and percentage of decrease of corneal diopter were significantly greater in control group compared to study groups. Topical therapy significantly reduced IOP in comparison to their respective pre-treatment IOP and to control group with non-significant difference between both groups. IOP lowering therapy is beneficial for amelioration of myopic regression after LASIK surgery manifested as improvement of DVA and lessening of spherical errors. Timolol 0.1% gel provided more efficient outcome compared to PG analogue and could be advocated for postoperative use.

Key words: LASIK, myopic regression, timolol gel, prostaglandin analogue

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INTRODUCTION

Excimer laser surgery has for years been a routine procedure for the correction of myopia, hyperopia and astigmatism. The LASIK surgery is generally preferred by patients and is currently the most common performed keratorefractive procedure. This preference could be attributed to the technical peculiarities of LASIK. In LASIK, the surgeon uses a microkeratome or femtosecond laser to create a flap of the corneal epithelium to access the underlying stromal tissue. Following excimer laser ablation of targeted stromal tissue to reshape the curvature of the corneal stroma, the flap is repositioned. This results in reduced pain and a quicker recovery in patients undergoing LASIK compared to those undergoing photorefractive keratectomy in which the central corneal epithelium is removed entirely (Shortt *et al*., 2006; Settas *et al*., 2012). However, myopic regression of the initial surgical effect can affect the predictability, efficiency and long-term stability of keratorefractive surgery, leading to deterioration in visual performance. The incidence of regression toward myopia after LASIK varies across studies, ranging from 5.5-27.7%. Actually, the mechanism for myopic regression still remains to be elucidated. Greater understanding of the mechanism for myopic regression that take place in the ocular tissue after surgery would help to improve the predictability and stability of achieved corrections (Randleman, 2006; Condon *et al*., 2007; Salgado *et al*., 2011).

Multiple studies reported a relationship between postoperative intraocular pressure and development of myopic regression and attributed this to the fact that increase in the internal pressure may expand and distend the cornea causing its anterior protrusion with subsequent myopic regression (Hsu *et al*., 2009; Qazi *et al*., 2009; Fan *et al*., 2012). Thus, the current study aimed to evaluate the effect of timolol 0.1% gel and latanoprost 0.005% on myopic regression after myopic LASIK surgery in comparison to artificial tears as placebo.

MATERIALS AND METHODS

The current comparative prospective study was conducted at LASIK Private Centers since June 2009 till June 2011 to allow a minimum follow-up period of 12 month for the last case enrolled in the study. After approval of study protocol by Local Ethical Committee and obtaining patients' fully informed written consent, 90 patients had normal ocular examination except for having undergone LASIK for myopia was included in the study. Exclusion criteria included any optical opacities or pathology on slit-lamp, previous ocular trauma or intraocular surgery, corneal disease or ocular infection; history of ocular disease or unavailability for follow-up.

All patients underwent complete ophthalmologic examination for determination of uncorrected and corrected distant visual acuity (UDVA and CDVA), Intraocular Pressure (IOP) measurement using a handheld applanation tonometer (Perkins, Edinburgh, Scotland), Schrimer test, central corneal pachymetry (Nidek Up-1000, Japan) and corneal topography (Optikon Keratron, Scout, Germany). The refractive power of the total cornea was averaged within a central zone of 3 mm diameter.

These parameters were evaluated at time of inclusion and 3 monthly for 12 months. The reported measures at the 12th month were considered as the final outcome and the percentage of change in comparison to the baseline measures was calculated for assurance of randomization and accurate evaluation of outcome.

Patients were randomly, using sealed envelops, allocated into 3 equal groups: Control group included 30 patients assigned to receive artificial tears as placebo; Timolol group included 30 patients assigned to receive timolol maleate 0.1% gel once daily and PG group included 30 patients assigned to receive latanoprost 0.005% eye drops once daily.

Statistical analysis: Obtained data was presented as Mean±SD, ranges, numbers and ratios. Results were analyzed using Wilcoxon ranked test for unrelated data (Z-test). Statistical analysis was conducted using the SPSS (2006) Version 15, for Windows statistical package. The $p<0.05$ was considered statistically significant.

RESULTS

The study included 90 patients with mean age of 25.7±5.7; range: 17-35 years. There were 51 males (56.7%) and 39 females (43.3%); 12 patients had bilateral LASIK and both eyes were included in the study, while 78 patients had unilateral LASIK and so the number of studied eyes was 102 eyes. There was non-significant ($p>0.05$) difference between studied groups as regards constitutional data or number of studied eyes (Table 1). Control eyes showed more regression of UCDVA at the end of follow-up, despite being non-significant ($p>0.05$) in comparison to baseline UCDVA. On contrary, both modalities of topical therapy significantly ($p<0.05$) improved UCDVA at the end of follow-up period as manifested by significant ($p<0.05$) improvement of UCDVA in both groups compared to control group and to their respective baseline UCDVA. Timolol group showed significantly ($p<0.05$) higher

Table 1: Patients' enrollment data

	Control group		Timolol group		PG group		Total	
Variables	No.	%	No.	%	No.	%	No.	%
Age (years)	24.7±6 (17-35)		26.5±5.9 (19-34)		26±5.2 (17-33)		25.7±5.7 (17-35)	
Gender								
Male	17	56.7	18	60.0	16	53.3	51	56.7
Female	13	43.3	12	40.0	14	46.7	39	43.3
Laterality								
Unilateral	25	83.3	26	86.7	27	90.0	78	86.7
Bilateral	5	16.7	4	13.3	3	30.0	12	13.3
Total number of eyes	35	34.3	34	33.3	33	32.4	102	100.0

Data is presented as Mean±SD and range is in parenthesis

Table 2: Patients' refractive data

Parameters	Control group (n = 35)	PG group (n = 34)	Timolol group (n = 33)
UCDVA			
Pre-treatment	0.383±0.045 (0.33-0.49)	0.367±0.039 (0.31-0.45)	0.380±0.058 (0.31-0.48)
Post-treatment	0.366±0.043 (0.31-0.45)	0.404±0.049*† (0.34-0.51)	0.485±0.075*† (0.37-0.64)
Change (%)	-4.34±1.69 (-8.57 to -2.22)	10.15±7.48* (0-20.6)	27.58±6.16*‡ (16.7-38.7)
CDVA			
Pre-treatment	0.625±0.045 (0.55-0.70)	0.618±0.046 (0.55-0.69)	0.626±0.05 (0.55-0.71)
Post-treatment	0.643±0.048 (0.58-0.72)	0.646±0.047† (0.58-0.72)	0.659±0.052† (0.58-0.74)
Change (%)	2.87±0.93 (1.47-4.62)	4.55±0.92* (3-6.15)	5.34±1.02*‡ (2.86-6.78)

Data is presented as Mean±SD, ranges are in parenthesis, UCDVA: Uncorrected distant visual acuity, CDVA: Corrected distant visual acuity, *Significant vs. control group, ‡Significant vs. PG group, †Significant vs. pre-treatment measures

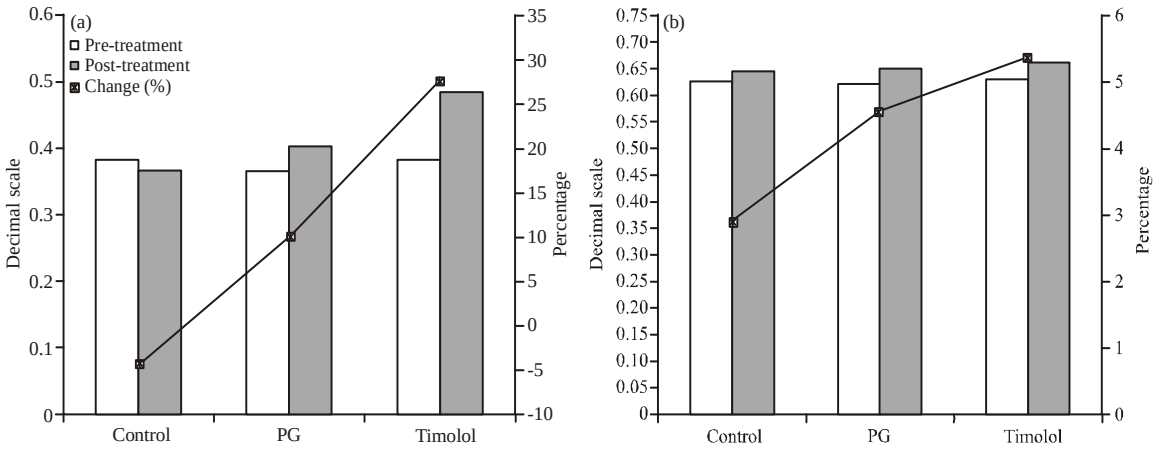

Fig. 1(a-b): Mean (a) UCDVA and (b) CDVA determined at the end of follow-up compared to baseline value with reference to percentage of change

percentage of improvement of UCDVA compared to PG group (Fig. 1a). As regards CDVA, control eyes showed a significantly ($p<0.05$) lower percentage of improvement at the end of follow-up compared to both other groups with significantly ($p<0.05$) higher percentage of improvement with timolol compared to PG (Table 2, Fig. 1b).

As regards spherical error evaluation and extent of astigmatism, control eyes showed non-significant ($p>0.05$) deterioration at the end of follow-up compared to baseline measures with a mean decrease of about 5 and 3%, respectively. On the other hand, both modalities of topical therapy significantly ($p<0.05$) improved both spherical equivalent and astigmatism at the end of follow-up period compared both to their respective preoperative measures and to control group. Timolol also, significantly ($p<0.05$) improved extent of astigmatism compared to PG with non-significant ($p>0.05$) improvement of spherical equivalent (Table 3, Fig. 2a, b).

Despite the non-significant ($p>0.05$) changes of corneal thickness and diopter in all studied patients till the end of follow-up period, the percentage of increase

Table 3: Patients' spherical error data

Parameters	Control group (n = 35)	PG group (n = 34)	Timolol group (n = 33)
Spherical equivalent (D)			
Pre-treatment	1.25±0.17 (1.02-1.54)	1.277±0.15 (1.06-1.61)	1.265±0.12 (1.09-1.56)
Post-treatment	1.319±0.19 (1.03-1.67)	1.13±0.12*† (0.92-1.37)	1.08±0.09*† (0.95-1.36)
Change (%)	5.46±3.6 (0-9.8)	-11.6±5.1* (-15.9-0)	-14.40±5.5* (-20- 0)
Astigmatism (D)			
Pre-treatment	0.928±0.11 (0.73-1.23)	0.967±0.15 (0.65-1.32)	0.978±0.14 (0.7-1.28)
Post-treatment	0.96±0.12 (0.73-1.28)	0.916±0.13*† (0.65-1.22)	0.9±0.11*† (0.68-1.14)
Change (%)	3.40±2.8 (0-11.5)	-5.2±2.8* (-9.7-0)	-7.8±4.2*‡ (-12.6-0)

Data is presented as Mean±SD, ranges are in parenthesis,*Significant vs. control group, ‡Significant vs. PG group, †Significant vs. pre-treatment measures

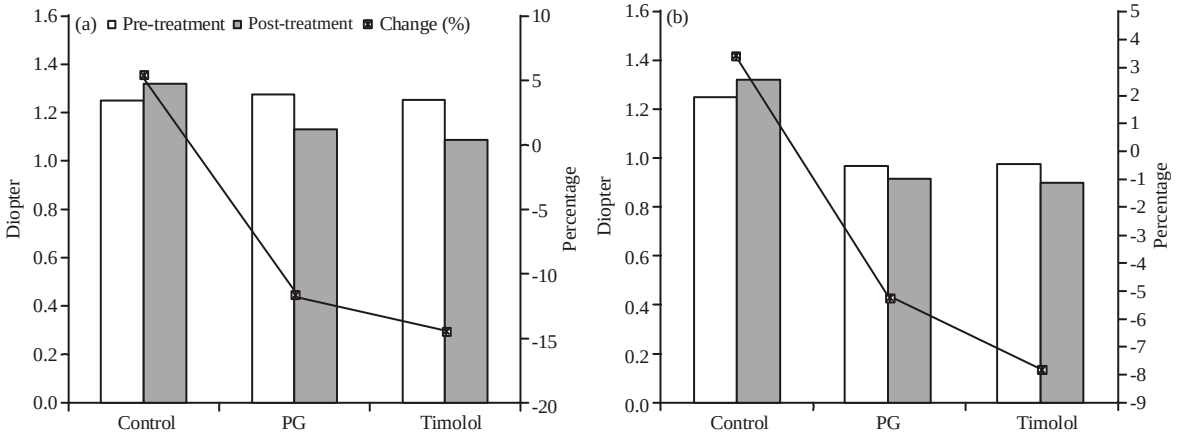

Fig. 2(a-b): Mean (a) Spherical equivalent and (b) Restent of astigmatism determined at end of follow-up compared of baseline value with reference to percentage of change

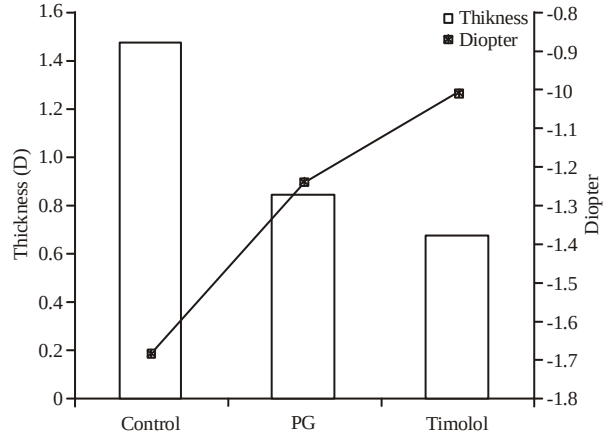

Fig. 3: Mean percentage of change of coneral measures determined at end of follow-up compared to baseline measures

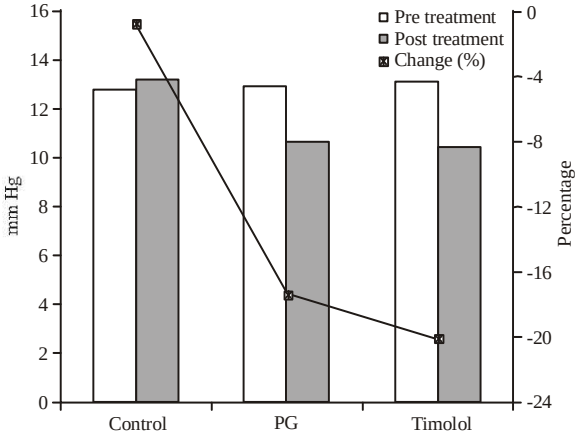

Fig. 4: Mean IOP measured at end of follow-up compared of baseline value with reference to percentage of change

of corneal thickness and percentage of decrease of corneal diopter were significantly ($p<0.05$) greater in control group compared to study groups with non-significant ($p>0.05$) difference of corneal thickness and diopter between PG and timolol groups, but in favor of timolol group (Table 4, Fig. 3).

Both lines of therapy significantly ($p<0.05$) reduced IOP in comparison to their respective pre-treatment IOP and to control group with non-significant ($p>0.05$) difference between both groups as regard IOP estimated at the end of 12 months follow-up (Table 5, Fig. 4).

Table 4: Patients' corneal thickness data

Parameters	Control group (n = 35)	PG group (n = 34)	Timolol group (n = 33)
Corneal thickness			
Pre-treatment	423.70±21.9 (375-454)	425.60±26.1 (380-465)	426.0±17.60 (390-454)
Post-treatment	429.90±21.4 (384-464)	429.20±26.6 (381-468)	429.0±17.80 (390-457)
Change (%)	1.47±0.96 (0-3.16)	0.84±0.61 (0-1.9)*	0.67±0.55 (0-1.6)*
Corneal diopter			
Pre-treatment	37.00±2.15 (34-41)	36.90±1.7 (34.5-39.4)	36.8±1.5 (33.9-39.5)
Post-treatment	36.40±2 (33.4-39.5)	36.50±1.8 (33.9-39.1)	36.4±1.6 (33.6-39.5)
Change (%)	-1.68±0.88 (-3.65 to)	-1.24±0.63 (-2.1 to 0)*	-1.0±0.6 (-1.68-0)*

Data is presented as Mean±SD, ranges are in parenthesis, *Significant vs. control group

Table 5: Patients' IOP data

Parameters	Control group (n = 35)	PG group (n = 34)	Timolol group (n = 33)
Pre-treatment	12.8±1.8 (10-17)	12.9±1.1 (11-15)	13.1±1.8 (10-16)
Post-treatment	12.6±1.2 (11-15)	10.6±0.9 (9-12)*†	10.4±1.2 (9-12)*†
Change (%)	-0.8±7 (-13.3-10)	-17.4±8.3 (-28.6 to -7.7)*	-20.1±9.5 (-30.8-9.1)*

Data is presented as Mean±SD, ranges are in parenthesis, *Significant vs. control group, †Significant vs. pre-treatment measures

DISCUSSION

The current study confirmed the need for a therapeutic means for prevention or amelioration of myopic regression after LASIK as reported in control group which showed a significantly higher percentage of both UCDVA and CDVA compared to both groups received topical therapy with concomitant significantly higher percentage of increased corneal thickness and diopter at the end of 12 months follow-up.

In support of these data, multiple studies tried technical modifications to improve the therapeutic yield of LASIK; Celik *et al.* (2012) tried accelerated corneal collagen cross-linking (CXL) applied concurrently with LASIK in four patients assigned for bilateral LASIK, LASIK with CXL in one eye and LASIK in the fellow eye and at the 12 month follow-up. The LASIK-CXL group had a UDVA and manifest refraction equal to or better than those in the LASIK group only, no eye lost 1 or more lines of CDVA at the final visit, the endothelial cell loss in the LASIK-CXL eye was not greater than in the fellow eye and concluded that accelerated CXL appears to be a promising modality for future applications to prevent corneal ectasia after LASIK treatment. However, there are limitations of this study; firstly the small sample population which could not provide grantee for the results, secondly the results did not confirm an advantage for LASIK-CXL over LASIK only. Also, Khoramnia *et al.* (2012) found LASIK with the prototype 1000 Hz excimer laser was safe, efficient and predictable with stable postoperative refraction over time. However, the limitation of this study was the short duration of postoperative follow-up which could not provide grantee for the results.

Topical PG therapy resulted in significant reduction of IOP compared to control group with reduction of myopic regression manifested as significantly improved refractive measures with significant limitation of increased spherical measurements. This data indicated the beneficial effects of using PG analogues as a conservative postoperative therapy for patients underwent LASIK. These findings go in hand with Qi *et al.* (2006) who reported that lowering the IOP preoperatively and postoperatively may be an effective way to prevent the myopic regression after LASIK and concluded that high preoperative IOP and the progressive postoperative biomechanical bowing in the posterior and anterior surfaces of the cornea, are two factors related to myopic regression. Kamiya *et al.* (2008) found that antiglaucoma drugs are effective for the reduction of the refractive regression, especially of the spherical errors, after LASIK and attributed flattening the corneal curvature to lowering the IOP and thus reduction of the IOP may contribute to improving regression after keratorefractive surgery.

Timolol provided significant preventive effect on myopic regression in comparison to control and PG groups and such beneficial effect was manifested as significant percentage of improvement of both UCDVA and CDVA with significant reduction of spherical measurement. In line with the efficacy of timolol, El-Awady *et al.* (2010) found timolol 0.1% gel was effective for reduction and improvement of myopic regression especially the spherical errors after myopic LASIK. However, there are limitations of this study; firstly the results relied on comparison to pre-treatment measures without comparison to control group to validate the results, secondly, the study showed increased mean corneal thickness in timolol group while decreased thickness in control group, a finding which is against the rational of the study. Zhang *et al.* (2011) assessed the preventive effects of early timolol eye drops application in patients after LASIK and reported significant difference between study and control group as regards

manifest refraction and IOP and concluded that timolol is effective to stabilize the refraction after LASIK and reduction of IOP and corneal ectasia may play a significant role in preventing myopic regression. Shojaei *et al.* (2012) compared the effects of timolol on refractive outcomes in eyes with myopic regression after LASIK with a control-matched group and found timolol application is effective for the treatment of myopic regression after LASIK compared with control group with its effects last for at least 6 months after its discontinuation.

The current study was more advantageous in that the reported stability was till 12 months follow-up period and use of gel not drops allowed prolonged contact with the applied material so it could explain the sustained effect.

Both therapeutic modalities did not significantly affect corneal thickness in relation to the pre-treatment and control data; despite the percentage of change was significantly lower in studied groups compared to control group. This data indicated a minimal or none effect of IOP lowering therapy on the proliferative power of keratinocytes which was evident in control group. In support of this data, Wierzbowska *et al.* (2009) found Central Corneal Thickness (CCT) appeared not to differ in eyes treated with different classes of antiglaucoma medications either in monotherapy or combined therapy and CCT of treated glaucoma eyes does not differ significantly from CCT of untreated glaucoma eyes. Birt *et al.* (2012) found a statistically significant association between a lower mean IOP and a thinner cornea when baseline IOP is controlled but the magnitude of the relationship is small.

The difference reported difference between the outcome using PG and timolol, but in favor of timolol could be attributed to the study of Bergonzi *et al.* (2010) who found keratocyte densities in the entire stroma and in 2 stromal layers were significantly higher in patients with PG analogue therapy compared with control patients and to β-adrenergic blocker patients with no significant differences between the control and β-adrenergic blocker groups.

CONCLUSION

It could be concluded that IOP lowering therapy is beneficial for amelioration of myopic regression after LASIK surgery manifested as improvement of DVA and lessening of spherical errors. Timolol 0.1% gel provided more efficient outcome compared to PG analogue and could be advocated for postoperative use. However, longer follow-up is mandatory for establishment of the obtained results.

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