International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2016.556.561

Research Article
Effects of Topical Brinzolamide/Timolol on Refractive Outcomes in Eyes with Myopic Regression after Corneal Refractive Surgeries

[1]Young Min Park, [2]Sang Ho Hwang, [3]Ji Woong Lee and [3]Jong Soo Lee

[1]Department of Ophthalmology, Gyeongsang National University School of Medicine, Gyeongsang National University Changwon Hospital, 11, Samjeongja-ro, Seongsan-gu, Changwon-si, Gyeongsangnam-do, 51472, South Korea
[2]Junggeun Eye Clinic, Pusan, South Korea
[3]Department of Ophthalmology, School of Medicine, Pusan National University and Medical Research Institute, Pusan National University Hospital, Pusan, South Korea

Abstract

Background and Objectives: To investigate the effects of topical brinzolamide/timolol on the inhibition of myopic regression after laser *in situ* keratomileusis (LASIK) and laser-assisted subepithelial keratomileusis (LASEK). **Methodology:** Sixty six eyes of 66 patients with myopic regression after corneal refractive surgery were classified into two groups: LASIK and LASEK group. All patients received topical brinzolamide/timolol twice a day for 2 months since the mean postoperative 6 months. Patients had complete eye examinations including Uncorrected Distance Visual Acuities (UDVA), intraocular pressure (IOP), anterior chamber angle and depth measurement, Spherical Equivalent (SE) and astigmatism with K value. **Results:** The value of IOP, SE and K at 1 and 2 months after the brinzolamide/timolol treatment were significantly reduced compared to the initial examination. The initial UDVA at 1 and 2 months after the treatment was markedly improved on the both groups. The angle and depth of anterior chamber were significantly changed for 2 months, although IOP, K value and SE reduction of both groups after the treatment for 2 months was markedly reduced. There was no significant difference in the effects of brinzolamide/timolol treatment between LASIK and LASEK group. **Conclusion:** Corneal biomechanical strength related factors including IOP, anterior chamber angle and depth are thought to be more responsible for the myopic regression. The improvement of myopic regression with brinzolamide/timolol treatment might be a result of the backward movement of the cornea and flattening of its curvature, which is presumably restricted to early treatment periods within 1 year.

Key words: Brinzolamide/timolol, LASEK, LASIK, myopic regression

Received: February 29, 2016 Accepted: April 07, 2016 Published: June 15, 2016

Citation: Young Min Park, Sang Ho Hwang, Ji Woong Lee and Jong Soo Lee, 2016. Effects of topical brinzolamide/timolol on refractive outcomes in eyes with myopic regression after corneal refractive surgeries. Int. J. Pharmacol., 12: 556-561.

Corresponding Author: Jong Soo Lee, Department of Ophthalmology, School of Medicine, Pusan National University and Medical Research Institute, Pusan National University Hospital, Pusan, South Korea, 1-10 Ami-dong, Seo-gu, Pusan 602-739, Republic of Korea
Tel: 82-51-240-7321 Fax: 82-51-242-7341

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Despite advances in excimer laser technology, up to 28% of the patients who had refractive surgery still experience myopic regression[1,2]. Forward shift of the cornea and postoperative increase in corneal thickness are considered major factors responsible for myopic regression after corneal refractive surgery with excimer laser[3,4]. As postoperative higher intraocular pressure (IOP) being important key for the forward shift of cornea[5-8], IOP reduction is thought to be an effective method for preventing myopic regression after refractive surgery[7,8]. However, there are no studies that evaluated the effect of IOP lowering agents on myopic regression between the various kinds of corneal ablation techniques related with excimer laser technology. The purpose of this study was to investigate the effects of topical brinzolamide/timolol on the correction of myopic regression and to compare the clinical outcome after the treatment of the patients who underwent laser *in situ* keratomileusis (LASIK) and laser-assisted subepithelial keratomileusis (LASEK).

MATERIALS AND METHODS

This study was conducted under the supervision of the Ethical Committee of the Pusan National University Hospital (IRB No. E-2014061) in accord with the tenets set forth in the Declaration of Helsinki. The charts of the patients with myopic regression after refractive surgery (LASIK or LASEK) were retrospectively reviewed (Fig. 1). All patients had same surgery on both eyes and had a monthly follow-up for at least postoperative 1 year. In order to avoid inter-eye interactions, only right eye of the patient was included. To avoid the possible instability of refraction, only patients beyond postoperative 3 months are included in this study. Myopic regression was defined as a 0.25 diopter (D) or greater myopic shift between follow-up visits 1 month postoperatively. Under-correction is defined as failure to achieve within 1.00 D or greater of the intended correction by 1 week postoperatively; patients meeting this criteria were excluded from the study. Patients with a history of refractive surgery retreatment, previous ocular surgery other than LASIK or LASEK, keratoconus or any ectatic corneal disorder, keratoconus suspect by topography, preoperative corneal opacity, any corneal dystrophy, presence of pterygium, retinal disorders, collagen vascular disorders, ocular inflammatory conditions, diabetes mellitus, glaucoma, cataract, pregnancy, breastfeeding and receiving systemic corticosteroid therapy were excluded. Also, patients with asthma or chronic bronchitis, diabetes, dysrhythmia, heart failure and any other conditions that are contraindicated to use beta-blockers were excluded.

All patients underwent refractive surgery with LADARvison 4000 excimer laser (Alcon Surgical, Orlando, FL, USA) using standard methods. Topical anesthesia was performed with 0.5% proparacaine hydrochloride (Alcaine; Alcon, Fort Worth, TX, USA). Lamellar keratotomy was performed in patients who received LASIK using a M2 microkeratome (Moria, Antony, France) to create an intended 160 μm flap thickness with a superior hinge. In contrast, flap-off procedures were performed in patients who received LASEK. A 20% ethyl alcohol solution diluted with distilled

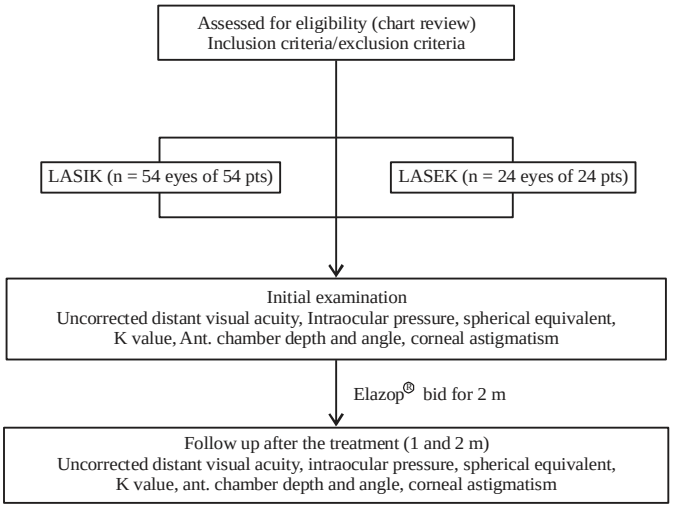

Fig. 1: Flow-chart of this study. Patients with myopic regression were classified into two groups: LASIK and LASEK group. All patients received brinzolamide/timolol twice a day for 2 months and were followed up on a monthly basis for 2 months

water was filled inside an 8.5 mm retaining well centered on the trephine mark and was left for 40 sec. The solution was removed with a merocel sponge and the eye was rinsed with balanced salt solution. An epithelial flap with a 12 O'clock hinge was created with a modified spatula. The optical zone was 6.0-6.5 mm based on the corneal thickness and curvature. In all eyes, attempted correction was aimed at emmetropia. All surgical procedures were performed by one surgeon (Dr. SHH). Patients were given levofloxacin eye drops (Cravit®; Santen pharmaceutical, Osaka, Japan) four times daily for the first postoperative week. Fluorometholone eye drops (Santen pharmaceutical) four times daily were administered when re-epithelization was complete and were then tapered over the following 4 weeks.

Patients were classified into two groups with myopic regression after receiving excimer laser technology according to surgery modality: LASIK and LASEK group. All patients received brinzolamide/timolol (Elazop; Alcon Laboratories Inc., Fort Worth, TX, USA) twice a day for 2 months and were followed up on a monthly basis for 2 months after the application of eye drops. The mean interval between Excimer laser surgery and IOP lowering treatment was about 6 months on the both group. All patients had thorough, eye examinations including Uncorrected Distance Visual Acuity (UDVA), slit-lamp examination, IOP measurement with Goldmann applanation tonometry, anterior chamber angle and depth measurement by scheimpflug imaging (Wavelight oculyzer II®, Alcon Surgical), auto-keratometery (RK-5®, Canon, Tokyo, Japan) and fundus examination. Anterior chamber depth is defined as distance between corneal endothelium to anterior lens surface. All measurements were carried out by one experienced optometrist with the same devices throughout the study.

The SPSS version 12.0 (SPSS, Chicago, IL, USA) was used for statistical analyses. The normality of numerical data distribution was checked with the Kolmogorov-Smirnov test. Due to the small sample size, the data did not show normal distribution. Parameters at baseline and between treatments were compared by repeated-measures analysis of variance (ANOVA) with the patient's eye as a within-subject variable in each LASEK and LASIK group. A paired t test was used to compare each time point within the ANOVA. Bonferroni's correction was used to adjust the p-values for multiple comparisons. Mann-Whitney U test was used to compare the results between the groups. The $p<0.05$ were considered statistically significant.

RESULTS

Sixty six eyes of 66 patients with myopic regression (44 eyes in LASIK group and 22 eyes in LASEK group) were included in this study (Table 1). The changes in IOP, Spherical Equivalent (SE) and K value after the brinzolamide/timolol treatment are listed in Table 2. Both groups showed a

Table 1: Demographic baseline characteristics of patients between LASIK and LASEK group

	LASIK group	LASEK group	p-value
Age (year)	37.23±6.15	32.00±8.56	0.15
Male/female	16/28	6/16	0.55
Regression (diopter)	-1.49±1.50 (-0.25 to -6.0)	-1.45±1.86 (-0.25 to -5.5)	0.92
Corneal astigmatism (diopter)	-0.51±0.57 (0 to -2.25)	-0.35±0.45 (0 to -2.0)	0.82
Residual stromal bed after refractive surgery (um)	291.67±45.13 (234 to 375)	334.75±44.77 (234 to 380)	0.10
UDVA (LogMAR)	0.25±0.47 (-0.17 to 1.0)	0.15±0.44 (-1.0 to -0.08)	0.30
Interval between surgery and IOP-lowering treatment (months)	6.73±2.76 (4.0 to 12.0)	7.04±2.26 (4.0 to 15.0)	0.45

Values are presented by Mean±SD (Range), LASIK: Laser *in situ* keratomileusis, LASEK: Laser-assisted subepithelial keratomileusis and UDVA: Uncorrected distance visual

Table 2: Intraocular pressure, spherical equivalent and K-value in patients between LASIK and LASEK group for 2 months

		Pretreatment	1 m	2 m
IOP (mmHg)	LASIK group	13.70±1.90	11.79±1.60	11.50±1.19
p-value			p = 0.004†	p = 0.000‡
	LASEK group	13.15±2.64	10.92±2.62	11.80±2.96
			p = 0.000†	p = 0.000‡
SE (Diopter)	LASIK group	-1.71±1.60	-0.80±1.16	-1.01±1.44
p-value			p = 0.000†	p = 0.000‡
	LASEK group	-1.65±1.60	-0.85±1.43	-0.55±1.46
			p = 0.000†	p = 0.000‡
K (Diopter)	LASIK group	39.63±1.55	39.24±3.12	38.00±3.42
p-value			p = 0.049†	p = 0.000‡
	LASEK group	40.00±2.89	39.43±2.17	38.17±2.11
			p = 0.030†	p = 0.000‡

†Bonferroni corrected p-value between baseline and 1 month, ‡Bonferroni corrected p-value between baseline and 2 month, no significant differences in initial IOP, SE or K-value were found between the two groups throughout the post-treatment period (Mann-Whitney U test, inter-group comparison), LASIK: Laser *in situ* keratomileusis, LASEK: Laser-assisted subepithelial keratomileusis, IOP: Intraocular pressure and SE: Spherical equivalent

Table 3: Anterior chamber depth and angle, corneal astigmatism and UDVA in patients between LASIK and LASEK group for 2 months

		Pretreatment	1 m	2 m
Anterior	LASIK group	3.20±0.32	3.10±0.23	3.02±0.34
Chamber			p = 0.025†	p = 0.000‡
Depth (mm)	LASEK group	3.24±0.38	3.21±0.40	3.21±0.20
p-value			p = 0.001†	p = 0.001‡
Anterior	LASIK group	36.52±4.09	37.01±4.29	37.51±2.29
Chamber			p = 0.038†	p = 0.014‡
Angle (°)	LASEK group	37.17±4.24	37.80±5.17	37.94±3.40
p-value			p = 0.043†	p = 0.046‡
Corneal	LASIK group	-0.51±0.57	-0.39±0.50	-0.43±0.22
Astigmatism			p = 0.482†	p = 0.541‡
Diopter	LASEK group	-0.35±0.45	-0.35±0.43	-0.25±0.39
p-value			p = 0.972†	p = 0.514‡
UDVA	LASIK group	0.25±0.47	0.11±0.47	0.00±0.10
			p = 0.000†	p = 0.000‡
logMAR	LASEK group	0.15±0.44	0.03±0.26	0.02±0.36
p-value			p = 0.000†	p = 0.000‡

†Bonferroni corrected p-value between baseline and 1 month, ‡Bonferroni corrected p-value between baseline and 2 months, no significant differences in initial anterior chamber angle and depth, corneal astigmatism or UCDA were found between the two groups throughout the post-treatment period (Mann-Whitney U test, inter-group comparison), LASIK: Laser *in situ* keratomileusis, LASEK: Laser-assisted subepithelial keratomileusis, IOP: Intraocular pressure and UDVA: Uncorrected distance visual acuity

significant decrease in IOP, K value and improvement in SE at 1 and 2 months after brinzolamide/timolol treatment versus initial examination. There was no significant difference in IOP, SE and K value between the LASIK and LASEK group throughout the post-treatment periods, respectively.

Table 3 shows the results of anterior chamber angle, anterior chamber depth and corneal astigmatism measurements with Scheimpflug imaging. The anterior chamber angle and depth increased significantly both in LASIK and LASEK group at 1 and 2 months after brinzolamide/timolol treatment versus initial examination. The astigmatism did not change significantly in both groups after brinzolamide/timolol treatment for 2 months. There was no significant difference in anterior chamber angle and depth, or corneal astigmatism between two groups during follow up periods. The UDVA improved significantly in both LASIK and LASEK groups at 1 and 2 months after brinzolamide/timolol treatment. Mean±SD UDVA (LogMAR) of LASIK group improved from 0.25±0.47 at baseline visit to 0.11±0.47 at post-treatment 1 month (p = 0.000) and further improved to 0.00±0.10 at post-treatment 2 months (p = 0.000). Mean±SD UDVA of LASEK group also improved from 0.15±0.44 at baseline visit to 0.03±0.26 at post-treatment 1 month (p = 0.000) and 0.02±0.36 at post-treatment 2 months (p = 0.000). There was no significant difference in UDVA between two groups during the follow-up periods.

DISCUSSION

A number of factors have been reported to be associated with myopic regression after LASIK, including preoperative refraction, preoperative keratometry, corneal thickness, flap thickness, ablation depth, optical zone size, chronic dry eye, age, IOP and postoperative undercorrection[9]. Miyata *et al.*[5] suggested postoperative forward shift of both corneal surfaces as the reason for myopic regression. Due to high postoperative IOP being the one of the important risk factors for the forward shift of the cornea[5-8], Kamiya *et al.*[8] reported that ocular hypotensive eye drops are effective for the reduction of refractive regression.

Brinzolamide 1% and timolol 0.5% are generally well tolerated and effective for lowering IOP[10]. The fixed combination of brinzolamide and timolol achieved greater IOP reductions than either brinzolamide or timolol monotherapy in patients with open-angle glaucoma or ocular hypertension[11]. Moreover, brinzolamide/timolol suspension provides statistically significant IOP-lowering efficacy that is non-inferior to dorzolamide/timolol and affords an ocular comfort advantage compared with dorzolamide/timolol[12]. There are several studies which have reported timolol to be effective for reduction and improvement of myopic regression[13,14]. Although, there are many reports that brinzolamide/timolol is effective in reducing intraocular pressure as compared to timolol[11], there are few studies on the effect of brinzolamide/timolol on myopic regression. For these reasons, this study was designed to evaluate the effect of brinzolamide/timolol on the improvement of myopic regression. Also, current study was designed to reveal the effect of ocular hypotensive eye drops on reducing the forward shifting of the corneal surface and to identify ocular factors associated with the treatment effect with respect to LASIK and LASEK group.

The IOP-lowering efficacy of brinzolamide/timolol was maintained during the follow-up periods. After 1 month of brinzolamide/timolol treatment, SE reduced by 0.41±1.60 diopter (D) per 1 mmHg decrease of IOP in the LASIK group and 0.24±0.62 D per 1 mmHg decrease of IOP in the LASEK group. The IOP was measured with a Goldmann applanation tonometer, which was considered to underestimate the actual IOP about 0.02-0.07 mmHg per 10 μm of corneal thickness after refractive surgery[15]. Thus, the true IOP presumably was higher than the readings in the current study. As current study only considered the range of IOP change before and after brinzolamide/timolol treatment, IOP compensation for corneal thickness was not performed.

Furthermore, the reduction in SE and K value also remained significant during the follow-up period in both groups. Along with the decrease in SE, a significant increase in anterior chamber angle and significant decrease in anterior chamber depth were observed during the follow-up period after brinzolamide/timolol treatment. The arc length of the cornea is constant regardless of IOP change. However, arc curvature change induced by IOP reduction occurs mainly on the thinnest portion of cornea, which is the central cornea in post-refractive eyes. This presumption is supported by the fact that a significant decrease in K value was observed in both groups after brinzolamide/timolol treatment. Backward shift of the central cornea led to decrease in anterior chamber depth and passive forward shift of the peripheral cornea, which caused increase in anterior chamber angle. This finding corroborates the previous study by Cairns *et al.*[16] who reported that the forward protrusion of the posterior corneal surface appears to coincide with a paradoxical reduction in depth of the anterior chamber. Nishimura *et al.*[17] also noted that central anterior chamber and volume decreased significantly after LASIK. Considering that both surfaces of cornea should bulge out equally, the anterior surface exerts far greater absolute refractive change than does the posterior surface, because the former faces air and the latter is in contact with the aqueous humor[5]. Far more refractive change in the corneal anterior surface might have played a role in retaining the SE reduction.

Mean interval between corneal refractive surgery and IOP-lowering treatment in this study was 6 months in LASIK group and 7 months in LASEK group. As post-refractive surgery corneas are known to show significant changes during the first postoperative year and it stabilizes afterwards[4,18], the effect of brinzolamide/timolol treatment on myopic regression can be limited. The biomechanical strength of the cornea can be substantially weakened by stromal tissue reduction during the early periods following corneal refractive surgery[7]. Among the entire layer of the cornea, only Bowman's layer and the stroma are known to contain collagen fibrils. As these two layers provide the majority of the cornea's tensile strength, the commencement of stromal remodeling after the refractive surgery might have promoted the restoration of corneal tensile strength. Hiatt *et al.*[7] also reported that IOP-lowering agents has only temporary effect of on myopic regression. However, Shojaei *et al.*[14] reported that timolol application is effective for the improvement of myopic regression after LASIK compared with a control group and its effects last for at least 6 months after discontinuation. Further study is, therefore in progress to confirm the long-term effect of brinzolamide/timolol treatment on myopic regression after refractive surgery.

As for IOP lowering effect, topical carbonic anhydrase inhibitors have possible side effects on corneal endothelium and the changes in corneal endothelial function might affect the corneal stromal hydration which results in myopic regression[19]. Thus, follow-up studies might be needed on the corneal stromal and endothelial function and morphology such as measuring the intrastromal corneal pressure, visualizing the endothelium with confocal microscopy[19,20].

CONCLUSION

This study showed that there was no significant difference between the effects of brinzolamide/timolol treatment with respect to LASIK versus LASEK. Actually, corneal biomechanical strength related factors including IOP and anterior chamber angle and depth are thought to be more responsible for the myopic regression than the surgical modality. The temporary improvement of myopic regression by brinzolamide/timolol treatment might be a result of the backward movement of the cornea and flattening of its curvature. The limitations of this study are that follow-up time is short and that the study is retrospective and lack of control group. Further studies with the prospective design and the control group are needed to evaluate the long term effect of brinzolamide/timolol treatment with excimer corneal refractive surgery. Succeeding studies should also consider the anterior chamber related factors such as corneal thickness and pupil size as they can be affected by antiglaucoma treatments.

REFERENCES

1. Park, Y.M., Y.K. Park, J.E. Lee and J.S. Lee, 2016. Effect of orthokeratology in patients with myopic regression after refractive surgery. Contact Lens Anterior Eye, 39: 167-171.

2. Wang, X., G. Zhao, J. Lin, N. Jiang, Q. Wang and Q. Xu, 2015. Efficacy and safety of topical timolol eye drops in the treatment of myopic regression after laser *in situ* keratomileusis: A systematic review and meta-analysis. J. Ophthalmol. 10.1155/2015/985071
3. Kamiya, K., K. Miyata, T. Tokunaga, T. Kiuchi, T. Hiraoka and T. Oshika, 2004. Structural analysis of the cornea using scanning-slit corneal topography in eyes undergoing excimer laser refractive surgery. Cornea, 23: S59-S64.
4. Ivarsen, A., W. Fledelius and J.O. Hjortdal, 2009. Three-year changes in epithelial and stromal thickness after PRK or LASIK for high myopia. Invest. Ophthalmol. Visual Sci., 50: 2061-2066.
5. Miyata, K., K. Kamiya, T. Takahashi, T. Tanabe, T. Tokunaga, S. Amano and T. Oshika, 2002. Time course of changes in corneal forward shift after excimer laser photorefractive keratectomy. Arch. Ophthalmol., 120: 896-900.
6. Kamiya, K. and T. Oshika, 2003. Corneal forward shift after excimer laser keratorefractive surgery. Semin. Ophthalmol., 18: 17-22.
7. Hiatt, J.A., B.S.B. Wachler and C. Grant, 2005. Reversal of laser *in situ* keratomileusis-induced ectasia with intraocular pressure reduction. J. Cataract Refractive Surg., 31: 1652-1655.
8. Kamiya, K., D. Aizawa, A. Igarashi, M. Komatsu and K. Shimizu, 2008. Effects of antiglaucoma drugs on refractive outcomes in eyes with myopic regression after laser *in situ* keratomileusis. Am. J. Ophthalmol., 145: 233-238.
9. Chen, Y.I., K.L. Chien, I.J. Wang, A.M.F. Yen, L.S. Chen, P.J. Lin and T.H.H. Chen, 2007. An interval-censored model for predicting myopic regression after laser *in situ* keratomileusis. Invest. Ophthalmol. Visual Sci., 48: 3516-3523.
10. Shedden, A., J. Laurence and R. Tipping, 2001. Efficacy and tolerability of timolol maleate ophthalmic gel-forming solution versus timolol ophthalmic solution in adults with open-angle glaucoma or ocular hypertension: A six-month, double-masked, multicenter study. Clin. Therapeut., 23: 440-450.
11. Kaback, M., S.V. Scoper, G. Arzeno, J.E. James and S.Y. Hua *et al*., 2008. Intraocular pressure-lowering efficacy of brinzolamide 1%/timolol 0.5% fixed combination compared with brinzolamide 1% and timolol 0.5%. Ophthalmology, 115: 1728-1734.
12. Manni, G., P. Denis, P. Chew, E.D. Sharpe and S. Orengo-Nania *et al*., 2009. The safety and efficacy of brinzolamide 1%/timolol 0.5% fixed combination versus dorzolamide 2%/timolol 0.5% in patients with open-angle glaucoma or ocular hypertension. J. Glaucoma, 18: 293-300.
13. El-Awady, H.E., A.A. Ghanem and M.A. Gad, 2010. Evaluation of the role of timolol 0.1% gel in myopic regression after laser *in situ* keratomileusis. Saudi J. Ophthalmol., 24: 81-86.
14. Shojaei, A., M. Eslani, Y. Vali, M. Mansouri, N. Dadman and M. Yaseri, 2012. Effect of timolol on refractive outcomes in eyes with myopic regression after laser *in situ* keratomileusis: A prospective randomized clinical trial. Am. J. Ophthalmol., 154: 790-798.
15. Whitacre, M.M., R.A. Stein and K. Hassanein, 1993. The effect of corneal thickness on applanation tonometry. Am. J. Ophthalmol., 115: 592-596.
16. Cairns, G., S.E. Ormonde, T. Gray, O.B. Hadden, T. Morris, P. Ring and C.N. McGhee, 2005. Assessing the accuracy of Orbscan II post LASIK: Apparent keratectasia is paradoxically associated with anterior chamber depth reduction in successful procedures. Clin. Exp. Ophthalmol., 33: 147-152.
17. Nishimura, R., K. Negishi, M. Dogru, M. Saiki and H. Arai *et al*., 2009. Effect of age on changes in anterior chamber depth and volume after laser *in situ* keratomileusis. J. Cataract Refractive Surg., 35: 1868-1872.
18. Alio, J.L., F. Soria, A. Abbouda and P. Pena-Garcia, 2015. Laser *in situ* keratomileusis for -6.00 to -18.00 diopters of myopia and up to -5.00 diopters of astigmatism: 15-year follow-up. J. Cataract Refract. Surg., 41: 33-40.
19. Teus, M.A., G. Bolivar, J.L. Alio and I. Lipshitz, 2009. Short-term effect of topical dorzolamide hydrochloride on intrastromal corneal pressure in rabbit corneas *in vivo*. Cornea, 28: 206-210.
20. Bolivar, G., M.A. Teus and J.L. Hernandez-Verdejo, 2010. Short-term effect of topical brimonidine tartrate on intrastromal corneal pressure in rabbits. J. Refractive Surg., 26: 533-535.