

Intraocular Pressure Lowering Effect of Single Dose Timolol, Brimonidine and Latanoprost on Different Ages of Normotensive Volunteers*

Tek Doz Timolol, Brimonidine ve Latanoprost'un Farklı Yaşlardaki Normotansif Gönüllülerde Göz İçi Basıncını Düşürme Etkinliği

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ABSTARCT

Purpose: The aim of the study is to evaluate the difference between intraocular pressure (IOP) peak lowering effect of single dose topical timolol maleat, latanoprost and brimonidine tartarate on healthy people with different age groups.

Materials and Methods: Eighty-nine eyes of 89 healthy volunteers were included. The patients younger than 51 years old were classified as group I and older than 64 years old were classified as group II. The patients were instilled a single drop of timolol maleat, brimonidine tartrate and latanoprost randomly. After evaluation for one drug a washout period of 1 week was allowed before second drug was evaluated. After baseline measurements, IOP measurements were repeated 2 hours after instillation of timolol and brimonidine drops and 12 hours after latanoprost drop.

Results: A single drop of each three drugs were found to be effective in IOP-lowering both in two groups. There were no statistically significant difference in IOP change between three drugs in group I, whereas there were statistically significant difference in group II. The differences between the effects of both timolol and brimonidine on two groups were statistically insignificant. The IOP reducing effect of latanoprost was 3.5 ± 2.0 mmHg in group I and 2.5 ± 2.4 mmHg in group II ($p=0.007$). There was a negative correlation between age and IOP reduction in latanoprost group ($p=0.002$), but no correlation was found in other two drugs.

Conclusion: Single doses of timolol, brimonidine and latanoprost have similar IOP-lowering effects in younger subjects. Timolol and brimonidine seemed to be more effective than latanoprost in reducing IOP in older cases.

Key-Words: Timolol, brimonidine, latanoprost, IOP-lowering effect, age, single dose.

ÖZ

Amaç: Farklı yaş gruplarındaki sağlıklı bireylerde tek doz timolol maleat, latanoprost ve brimonidin tartarate damlanın göz içi basıncı (GİB) düşürmedeki etkinliğinde fark olup olmadığını araştırmak.

Gereç ve Yöntem: Seksen dokuz sağlıklı gönüllünün 89 gözü çalışmaya alındı. Elli bir yaşın altındaki bireyler grup I; 64 yaşın üstündeki bireyler grup II olarak sınıflandırıldı. Olgulara rastgele sırayla tek doz timolol maleat, brimonidin tartrat ve latanoprost damlatıldı. Her ilaç uygulamasından sonra diğer ilacı damlatmadan önce 1 hafta beklendi. Damla öncesi GİB ölçümünü takiben timolol ve brimonidin damlattıktan 2 saat sonra, latanoprost damlattıktan 12 saat sonra GİB ölçümleri tekrarlandı.

Bulgular: Her üç ilacın da tek dozunun, her iki grupta da GİB düşürmede etkin olduğu saptandı. İlaçlar arasında, damla sonrası GİB değişimi açısından Grup I'de fark saptanmamasına rağmen grup II'de anlamlı fark bulundu. Grup I'de üç ilaç arasında GİB düşürücü etki açısından fark bulunmazken, grup II'de anlamlı fark saptandı. Grup I ve II'de timolol ve brimonidin etkileri açısından anlamlı fark bulunmadı. Buna karşılık latanoprost ile grup I'de 3.5 ± 2.0 mmHg; grup II'de 2.5 ± 2.4 mmHg GİB düşüşü elde edildi ($p=0.007$). Latanoprost grubunda GİB düşüşü ile yaş arasında negative korelasyon saptanırken ($p=0.002$), diğer iki ilaçta anlamlı korelasyon bulunamadı.

Sonuç: Timolol, brimonidin ve latanoprost genç bireylerde benzer GİB düşürücü etkiye sahiptir. Timolol and brimonidin, yaşlı bireylerde GİB'i düşürmede latanoprosttan daha etkin gibi görünmektedir.

Anahtar Kelimeler: Timolol, brimonidin, latanoprost, GİB düşürücü etki, yaş, tek doz.

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INTRODUCTION

Glaucoma is one of the most common causes of irreversible blindness worldwide. Elevated intraocular pressure (IOP) is an important risk factor for glaucoma and lowering IOP is effective in delaying or preventing glaucomatous optic nerve damage. Throughout last 30 years, many effective anti-glaucomatous agents have been introduced, including β -blocking agents, prostaglandin analogs, topical and oral carbonic anhydrase inhibitors and α -agonists.¹ Latanoprost, timolol and brimonidine are widely used and each was shown to be effective as ocular hypotensive drugs.^{2,3} A meta-analysis confirmed that latanoprost, timolol and brimonidine significantly reduced IOP in patients with normal tension glaucoma.⁴

Many clinical trials were published to evaluate the efficacy of these medications.³⁻⁸ However, the results of these studies suggested that there was controversy as to the degree of reduction of IOP that can be achieved with different drugs.⁴ Despite the demonstrated ocular hypotensive efficacy of medications used in glaucoma therapy, specific analyses of rate of response have not been included in any publication.⁵ Also it has not been studied how difference in baseline characteristics such as age could explain variations in the IOP reduction after treatment with antiglaucomatous drugs. Sometimes, single dose of antiglaucoma medications may be needed to use for prophylaxis in people without glaucoma. One of the most common complication after intraocular surgery or laser such as YAG-laser capsulotomy is postoperative IOP elevation in eyes without preexisting glaucoma. There are several studies that investigated a single drop of anti-glaucomatous agent efficacy before procedure in preventing IOP elevation in non-glaucomatous patients.⁹⁻¹¹

The aim of this prospective study was to determine whether there was a difference between IOP peak lowering effect of single dose of three commonly used topical antiglaucomatous agents on different ages of healthy volunteers.

MATERIALS AND METHODS

This prospective, cross-sectional and comparative study was performed at the Beyoglu Eye Training and Research Hospital. The study followed the tenets of the Declaration of Helsinki and was approved by the local ethics committee. All participants received oral and written information about the study and each participant provided written informed consent. In this study, a minimum sample of 39 eyes was necessary according to a mean of at least 1 unit and a standard deviation of 1.4 units for the estimated amount of reduction in IOP following 3 groups of drugs, ac-

cepting type 1 error at 0.05 and type 2 error at 0.20.

Eighty nine eyes of 89 healthy 18 years of age or older volunteers without any ocular or systemic medication were included in the study. Exclusion criteria were previous ocular surgery or trauma, pseudoexfoliation syndrome, pigment dispersion syndrome, glaucoma, ocular hypertension (IOP greater than 22 mmHg), myopia and hypermetropia greater than 3 D, current use of contact lenses, previous or active corneal diseases or any condition preventing reliable applanation tonometry. Also, a history of any active or chronic systemic disease, currently pregnant or nursing women were considered reasons for exclusion, as well as patients with a history of non-compliance and age between 51 and 64. If both eyes fulfilled the eligibility criteria, the right eye was designated as trial eye.

All the patients were offered a routine eye examination (best corrected visual acuity with Snellen chart (BCVA), biomicroscopy, Goldmann applanation tonometry (GAT), fundus examination with 90 D lens before participation. The IOP was measured with the same calibrated GAT by the same physician (IK) who was masked to the treatment assignment. Two consecutive readings were taken of the study eye and the average was recorded. Central corneal thickness (CCT) of patients were measured with ultrasonographic pachimetry (DGH-550, DGH Technology Inc., Exton, PA).

Intraocular Pressure Study

After inclusion into the study the patients were instilled a single drop of timolol maleate 0.5% (Timoptic®; MSD®; USA), brimonidine tartrate 0.2% (Alphagan®; Allergan®; USA) and latanoprost 0.005% (Xalatan, Pharmacia&Upjohn Company, Peapack, NJ, USA) randomly. Patients self-administered their study drugs. After evaluation for one drug a wash-out period of 1 week was allowed before second drug was evaluated.⁸ After baseline measurements at 8.00 am IOP measurements were repeated 2 hours after instillation of timolol and brimonidine (10 am, peak effects^{8,12,13}). However, latanoprost was given to the patients at around 22:00 pm and IOP measurement was repeated 12 hours after the application of latanoprost (10 am, peak effect²).

The study patients younger than 51 years old were classified as group I and older than 64 years old were classified as group II. Statistical analysis was performed SPSS 15.0 for Windows. Kolmogorov-Smirnov test was used to evaluate the normality of distribution for all the IOP measurement data for each group and drug subgroups within each group. The differences in IOP in the study eye before and after instillation of the drops were calculated and Wilcoxon Signed Rank Test were used for statistical analysis.

Table 1: The statistical analysis of the effectiveness of each medication on group I and group II.

Groups	Drugs	Before IOP	After IOP	Difference (%)	P1
Group 1 (n=45)	Timolol	15.1±2.7	11.1±2.2	4.1±1.8 (27.1%)	<0.001
	Latanoprost	15.3±2.7	11.7±2.5	3.5±2.0 (22.8%)	<0.001
	Brimonidine	14.6±2.7	10.9±2.6	3.7±1.9 (25.3%)	<0.001
	P2	0.21	0.19	0.42	<0.001
Group 2 (n=44)	Timolol	14.6±3.3	10.8±2.8	3.7±1.7 (25.3%)	<0.001
	Latanoprost	14.8±2.8	12.2±2.7	2.5±2.4 (16.9%)	<0.001
	Brimonidine	14.6±3.2	10.7±3.0	3.9±1.4 (26.7%)	<0.001
	P2	0.89	0.04	0.001	<0.001

P1: Wilcoxon Signed Rank Test, P2: Kruskal-Wallis Test).

Mann-Whitney U test was used to compare the difference of IOP between group I and II. Kruskal-Wallis Test was used to compare IOP-lowering effects of three drugs in group I and II. Mann-Whitney U test with Bonferroni correction was used as a Post-Hoc test to find the significantly different subgroup(s). The correlation between IOP decreases and age was evaluated by Spearman’s Rho coefficient. p value of less than 0.05 was considered statistically significant.

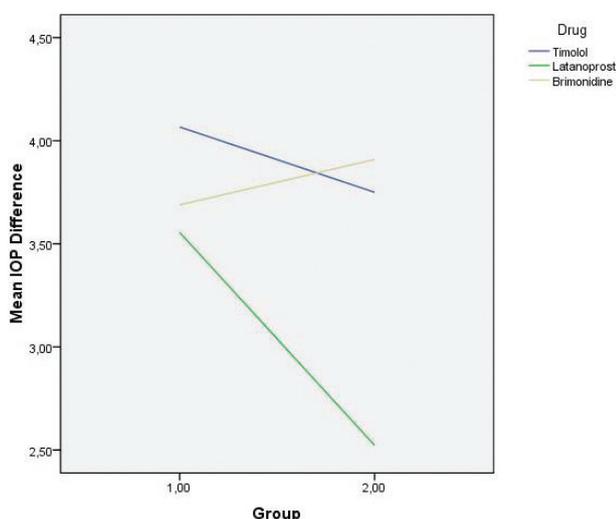
RESULTS

Eighty-nine eyes of 89 healthy patients were included in this study. There were 48 women and 41 men with a mean age of 53.6±16,3 years. The mean age of Group I was 39.3±9.3 (19-50) years and that of Group II was 68.4±3.5 (65-82) years. The mean BCVA was 0.97±0.05 in group I and 0.94±0.08 in group II (p>0.05). The mean CCT was 546.8±29.6 μ in group I and 543.1±37.6 μ (p>0.05).

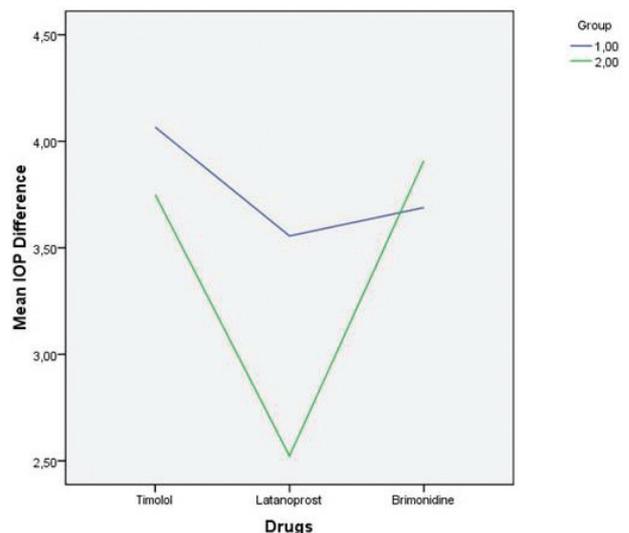
Changes in Intraocular Pressure

Table 1 shows the IOP measurements and differences before and after single dose instillation of three drugs in group I and II.

A single drop of each three drugs were found to be effective in IOP-lowering regardless of age (p<0.001), (Table 1, Graphic 1). There were no difference in IOP measurements before drops between group I and II and also between three of drug groups (p>0.05). There were no statistical difference in IOP change and IOP measurements after instillation of drops between three drugs in group I. Whereas there were statistically significant difference in IOP change and IOP measurements after instillation of drops between three drugs in group II (Kruskal-Wallis Test, Table I). Latanoprost was the drug that causes a statistically significant difference between measurements determined by post hoc test. Table 2 compares the effects of each individual drug between two groups. The differences between the effects of both timolol maleat and brimonidine tartrate on the two groups were statistically insignificant (p>0.05). The IOP reducing effect of latanoprost was 3.5±2.0 mmHg in Group I and 2.5±2.4 mmHg in Group II (p=0.007) (Table 2, Graphic 2). In correlation analysis, there was a negative correlation between age and IOP reduction in latanoprost group (p=0.002), but no correlation was found in other two drugs (p=0.45 for timolol, p=0.43 for brimonidine).



Graphic 1: The comparisons of the effectiveness of each medication on group I and group II.



Graphic 2: The comparisons of two groups in terms of IOP change with three drugs.

Table 2: The statistical analysis of the effectiveness of each medication between group I and group II.

Drugs	Groups and p values	Before IOP	After IOP	Difference (%)
Timolol	Group 1	15.1±2.7	11.1±2.2	4.1±1.8 (27.1%)
	Group 2	14.6±3.3	10.8±2.8	3.7±1.7 (25.3%)
	p	0.46	0.76	0.52
Latanoprost	Group 1	15.3±2.7	11.7±2.5	3.5±2.0 (22.8%)
	Group 2	14.8±2.8	12.2±2.7	2.5±2.4 (16.9%)
	p	0.23	0.5	0.007
Brimonidine	Group 1	14.6±2.7	10.9±2.6	3.7±1.9 (25.3%)
	Group 2	14.6±3.2	10.7±3.0	3.9±1.4 (26.7%)
	p	1	0.63	0.41

P: Mann-Whitney U test.

DISCUSSION

The IOP-lowering effects of anti-glaucomatous agents depend on drugs' ability to pass through the cornea and bind to receptors in the different tissues of eye. The drugs are able to pass through the cornea owing to the presence of enzymes such as amidase, peptidase and fatty acid hydrolases, and esterase.¹⁴⁻¹⁷ The efficacy of drugs occur with the ability of the drugs passing into the inner eye to bind to alpha, beta adrenergic receptors and FP receptors and to reorganize the extracellular matrix.¹⁸⁻²⁰ The cornea acts like a lipid-water-lipid sandwich. The epithelium and endothelium are readily transversed by lipid soluble substances, but are impermeable to water-soluble agents. Drugs tend to concentrate in the various layers of the cornea. Some of the drug may be degraded at this level, while another portion is temporarily stored in the cornea. Therefore, the cornea acts as a depot and a limiting factor for transfer of the drug to the aqueous humor. Having penetrated the cornea, the drug must now pass through the aqueous humor to the appropriate structures in the eye.²¹

Drugs presently used in glaucoma therapy alter the functions in the eye by direct interaction either with receptors or with certain specific enzymes.²² It is also worth considering that the degree of control of a particular response can vary with state of the tissue, such as in neonatal, geriatric or pathologic situations. These factors contribute to some of the problems in glaucoma research such as antiglaucoma drug development.²³ Timolol, a β -blocker, is known to reduce IOP by primarily reducing the rate of aqueous formation.²⁴ The action of beta blockers is related to that pharmacologic activity at beta adrenergic receptors.²²

Gupta et al.,⁸ showed that topical application of a single drop of timolol maleat produced first significant lowering of IOP in 1st hour and the peak IOP-lowering effect of 20% from baseline was observed at 2 hours posttreatment.

In this study, single dose of timolol brought about a statistically significant IOP reduction in both the younger and the older groups (27.1% and 25.3% respectively, $p > 0.05$); there was no difference in the effect of timolol in terms of age. Brimonidine tartrate is a relatively selective α_2 -specific agonist and a lipophilic drug. As with other highly lipophilic drugs, brimonidine's primary route of delivery is through the cornea. Postsynaptic α_2 -adrenergic receptors are mostly involved in the ocular responses to α_2 -agonists.²³ Brimonidine lowers IOP by suppressing aqueous humor production and increasing uveascleral outflow.^{22,25} Brimonidine has similar IOP-lowering effects to beta blockers.^{12,26,27} The peak reductions in IOP with brimonidine was measured 2 hours after morning dose in the studies.^{12,13} In this study brimonidine also was effective regardless of age (25.3% in group I and 26.7% in group II, $p > 0.05$). This results of age-independent effects of both timolol and brimonidine can be support the idea that as age increases, the effect of the α_2 adrenergic system on the vascular bed does not decrease and the adrenergic system does not lose its activity.^{21,23,27} Latanoprost is a prostaglandin (PG) analog that lowers IOP by increasing the aqueous outflow through the uveoscleral pathways secondary to relaxation of ciliary muscle and alteration of extracellular matrix (ECM) between the ciliary muscle bundles.^{8,28} Ciliary muscle contains several different PG receptors, mainly FP and EP2 receptors.

Activation of these receptors stimulates several linked responses, including cAMP formation and induction of nuclear regulatory proteins. These signals lead to increased biosynthesis of matrix metalloproteinases (MMPs), a family of secreted proteases that can cleave collagens and other extracellular structural proteins. In addition, there is reduction in the ciliary muscle content of the ECM molecules, collagen type I, III and IV. These responses increase spaces among ciliary muscle fibres, thereby reducing hydraulic resistance in the uveoscleral outflow pathway.^{19,20}

The sensitivity of PGF2 alpha receptors to latanoprost is different among individuals.^{15,16,29,30} Furthermore, during aging, changes occur in the structure of the ECM proteins and collagen, protein synthesis slows down, and intracellular enzymatic functions break down. The aging of ECM is characterized by an age-related increase in insolubilization, yellowing and stiffening, all of which can be mimicked by the Maillard reaction *in vitro*. These phenomena are accelerated by various glycation products and crosslinks.²¹ The aging mechanism of ECM includes age-dependent modifications of matrix biosynthesis, postsynthetic modifications of ECM, and modifications of cell-matrix interactions. These include the Maillard reaction, uncontrolled proteolytic degradation and free-radical release. Moreover, alteration of structure and function of elastin-laminine receptors with age are mentioned in the literature.²² Therefore, functional, active ECM and muscular structure are necessary for the efficacy of latanoprost. A single-drop application of latanoprost reduced IOP over the next 24 hours compared with placebo in healthy volunteers; the beginning of significant lowering effect was noted in 90th minutes and the maximal effect (20.4%) was noted in 12th hours.² Kiuchi et al.,³¹ studied latanoprost given as a single dose to healthy male volunteers, they showed that when latanoprost was administered in the evening the greatest IOP reduction was found 12 to 18 hours post-dose with IOP slowly returning to baseline values after 24 hours. In our study, we detected significantly IOP reduction after 12th hours of a single drop of latanoprost in healthy subjects in two groups. The difference of the IOP reducing effect of latanoprost was significant between the groups (3.5 ± 2.0 mmHg (22.8%) in Group I and 2.5 ± 2.4 mmHg (16.9%) in Group II, $p=0.007$) The reasons of this results are not clear. The anatomical difference of uveoscleral outflow pathway may cause to slightly less responsive to latanoprost in elder normotensive people. Besides, a higher proportion of latanoprost-treated patients was found to maintain or increase their treatment effect over time than the timolol-treated patients.^{5,7} It has been proposed that the increase in latanoprost's hypotensive effect occurring after weeks of treatment could be due to the requirement anatomic alterations of the ECM.^{1,5,7,28} It is possible that the mentioned anatomic alterations could be more less with aging. Treatment response differences between younger and older patients has not previously been reported with ocular hypotensive drugs. This is probably because the patient populations seldom are large enough to detect such small differences. But Hedman and Larsson compared the IOP reduction of latanoprost or timolol in a heterogeneous global population of 1389 patients.⁷ They found that there was a weak age trend regarding the difference in mean diurnal IOP reduction between the two

drugs ($p<0.05$). Latanoprost reduced mean diurnal IOP 2.4, 1.9, 1.0, and 1.3 mm Hg more than timolol in the age class of 18-49, 50-59, 60-69, and 70-95 years, respectively. Patients younger than 60 years of age showed a slightly larger difference in mean diurnal IOP reduction between latanoprost and timolol, in favor of latanoprost, as compared to the older patients.⁷ Another study reported that response to latanoprost showed individual differences regardless of age.³² Bayer et al. investigated the correlation between numerous clinical characteristics and IOP-lowering effect of latanoprost and they also found a weak inverse correlation with age and latanoprost treatment effect.³³ This is in contrast to Tamada et al who reported that latanoprost was more effective in older patients hypothesizing that aging of ciliary muscle may alter the effect of latanoprost by modifying uveoscleral outflow.³⁴ We were unable to find another study which compares the IOP-reducing effect of latanoprost, timolol and brimonidine in different age groups for healthy volunteers in the literature (Pubmed search). In current study, the IOP peak lowering-effects of single dose of three commonly used topical antiglaucomatous agents were assessed on healthy people by dividing to two groups keeping the age difference at least one decade. (Younger than 51 and older than 64). However, between 50 and 65 years age group is absent in this study. Would be incorrect to generalize the results of our study for glaucoma patients. We are of the opinion that further studies could be carried out about effects of anti-glaucomatous drugs in different age groups with glaucomatous and nonglaucomatous eyes. Another limitation of our study was that the measurements were taken at the same time delay following instillation only once. Although the IOP is subject to individual and diurnal variations, we assessed the medication effect at the time when peak effect was expected. The same measurement method was used for both groups.

In conclusion, the IOP peak lowering effects of timolol, brimonidine and latanoprost were sufficiently satisfactory after a single-dose administration in different ages group of normotensive subjects. Three of drugs have similar effects in young subjects. The peak IOP lowering effect of latanoprost was not different to that of timolol and brimonidine in the young group, but it was statistically significantly lower in the older group. There is a negative correlation between age and IOP reduction in latanoprost group ($p=0.002$), but no correlation was found in other two drugs. It is possible that single drop of latanoprost could not be stimulate uveoscleral pathway enough or rapidly due to alterations of enzyme and ECM metabolism in the older group. It might be more appropriate to use timolol or brimonidine when rapid and more effective IOP lowering needed for old normotensive people.

REFERENCES/KAYNAKLAR

1. Maeda-Chubachi T, Chi-Burris K, Simons BD, et al. Comparison of Latanoprost and Timolol in Pediatric Glaucoma: A Phase 3, 12-Week, Randomized, Double-Masked Multicenter Study. *Ophthalmology* 2011;118:2014-21.
2. Larsson LI. Intraocular pressure over 24 hours after single-dose administration of latanoprost 0.005% in healthy volunteers. A randomized, double-masked, placebo controlled, cross-over single center study. *Acta Ophthalmol Scand* 2001;79:567-71.
3. Sherwood MB, Craven ER, Chou C, et al. Twice-daily 0.2% brimonidine-0.5% timolol fixed-combination therapy vs monotherapy with timolol or brimonidine in patients with glaucoma or ocular hypertension: a 12-month randomized trial. *Arch Ophthalmol* 2006;124:1230-8.
4. Cheng JW, Cai JP, Wei RL. Meta-analysis of medical intervention for normal tension glaucoma. *Ophthalmology* 2009;116:1243-9.
5. Camras CB, Hedman K: US Latanoprost Study Group. Rate of response to latanoprost or timolol in patients with ocular hypertension or glaucoma. *J Glaucoma* 2003;12:466-9.
6. Choplin N, Bernstein P, Batoosingh AL, et al. Bimatoprost/Latanoprost Study Group. A randomized, investigator-masked comparison of diurnal responder rates with bimatoprost and latanoprost in the lowering of intraocular pressure. *Surv Ophthalmol* 2004;49:19-25.
7. Hedman K, Larsson LI. The effect of latanoprost compared with timolol in African-American, Asian, Caucasian, and Mexican open-angle glaucoma or ocular hypertensive patients. *Surv Ophthalmol* 2002;47:77-89.
8. Gupta SK, Agarwal R, Galpalli ND, et al. Comparative efficacy of pilocarpine, timolol and latanoprost in experimental models of glaucoma. *Methods Find Exp Clin Pharmacol* 2007;29:665-71.
9. Artunay O, Yuzbasioglu E, Unal M, et al. Bimatoprost 0.03% versus brimonidine 0.2% in the prevention of intraocular pressure spike following neodymium:Yttrium-Aluminum-Garnet Laser Posterior Capsulotomy. *J Ocul Pharmacol Ther* 2010;26:513-7.
10. Unal M, Yucel I. Effect of Bimatoprost on intraocular pressure after cataract surgery. *Can J Ophthalmol* 2008;43:712-6.
11. Chen TC, Ang RT, Grosskreutz CL, et al. Brimonidine 0.2% versus Apraclonidine 0.5% for Prevention of Intraocular Pressure Elevations after Anterior Segment Laser Surgery. *Ophthalmology* 2001;108:1033-8.
12. Adkins JC, Balfour JA. Brimonidine. A review of its pharmacological properties and clinical potential in the management of open angle glaucoma and ocular hypertension. *Drugs&Aging* 1998;12:226-41.
13. Greenfield DS, Liebmann JM, Ritch R. Brimonidine: a new alpha2-adrenoreceptor agonist for glaucoma treatment. *J Glaucoma* 1997;6:250-8.
14. Hellberg M, McLaughlin M, Sharif N, et al. Identification and characterization of the ocular hypotensive efficacy of travoprost, a potent and selective FP prostaglandin receptor agonist, and AL-6598, a DP prostaglandin receptor agonist. *Surv Ophthalmol* 2002;47:13-33.
15. Alexander CL, Miller SJ, Abel SR. Prostaglandin analog treatment of glaucoma and ocular hypertension. *Ann Pharmacother* 2002;36:504-11.
16. Sakurai M, Higashide T, Takahashi M, et al. Association between genetic polymorphisms of the prostaglandin F2alpha receptor gene and response to latanoprost. *Ophthalmology* 2007;114:1039-45.
17. Hennes S, Swainston Harrison T, Keating GM. Ocular carteolol: a review of its use in the management of glaucoma and ocular hypertension. *Drugs Aging* 2007;24:509-28.
18. Orengo-Nania S, Landry T, Von Tress M, et al. The Travoprost Study Group. Evaluation of travoprost as adjunctive therapy in patients with uncontrolled intraocular pressure while using timolol 0.5%. *Am J Ophthalmol* 2001;132:860-8.
19. Schachtschabel U, Lindsey JD, Weuireb RN. The mechanism of action of prostaglandins on uveoscleral outflow. *Curr Opin in Ophthalmol* 2000;11:112-15.
20. Marchini G, Chilott G, Banadiniani M, et al. Effects of 0,005% Latanaprost on ocular anterior structures and ciliary body thickness. *J Glaucoma* 2003;12:295-300.
21. Shields M.B. *Textbook of Glaucoma*. Baltimore, Williams and Wilkins, 1992:431-45.
22. Kaufman PL, Mittag TW. Medical therapy of glaucoma. In: Kaufman PL, Mittag TW editors. *Glaucoma*. London: Mooby-Yearbook 1994:9.7-9.30.
23. Mittag TW. Adrenergic and dopaminergic drugs in glaucoma. In: Rich R, Shields MB, Krupin T, editors. *The Glaucoma*, St Louis Mooby Year book 1996:1409-24.
24. Coakes RL, Brubaker RF. The mechanism of timolol in lowering intraocular pressure in the normal eye. *Arch Ophthalmol* 1978;96:2045-8.
25. Gieser SC, Juzych M, Robin AL, et al. Clinical Pharmacology of adrenergic drugs. In: Ritch R, Shields MB, Krupin T, editors. *The Glaucoma St. Louis Mooby Yearbook* 1996:1425-48.
26. İnan UU, Ermis SS, Orman A, et al. The comparative cardiovascular, pulmonary, ocular blood flow, and ocular hypotensive effects of topical travoprost, bimatoprost, brimonidine, and betaxolol. *J Ocul Pharmacol Ther* 2004;20:293-306.
27. Noecker RJ. Brimonidine 2% as a replacement for beta blockers in geriatric patients with glaucoma. *Adv Ther* 2002;19:91-7.
28. Lindsey JD, Kashiwagi K, Kashiwagi F, et al. Prostaglandin action on ciliary smooth muscle extracellular matrix metabolism: Implication for uveoscleral outflow. *Surv Ophthalmol* 1997;41:53-9.
29. Hedner J, Everts B, Möller CS. Latanoprost and respiratory function in asthmatic patients. *Arch Ophthalmol* 1999;117:1305-9.
30. Vuori ML, Melkkila TM, Kaila T, et al. Plasma and aqueous humour concentrations and systemic effects of topical betaxolol and timolol in man. *Acta Ophthalmol* 1993;71:201-6.
31. Kiuchi Y, Takamatsu M, Mishima HK. PhXA41 a prostaglandin F2 analogue reduces the intraocular pressure in human volunteers during day and night. *Invest Ophthalmol Vis Sci* 1994; 35:2178-84.
32. Scherer WJ. A retrospective review of non-responders to latanoprost. *J Ocul Pharmacol Ther* 2002;18:287-91.
33. Bayer A, Henderer JD, Kwak T, et al. Clinical predictors of latanoprost treatment effect. *J Glaucoma* 2005;14:260-3.
34. Tamada Y, Taniguchi T, Murase H, et al. Intraocular pressure-lowering efficacy of latanoprost in patients with normal-tension glaucoma or primary open-angle glaucoma. *J Ocul Pharmacol Ther* 2001;17:19-25.