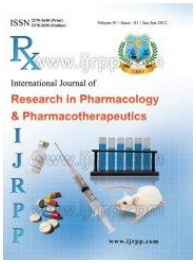
International Journal of Research in Pharmacology & Pharmacotherapeutics



ISSN Print: 2278-2648 ***IJRPP |Vol.6 | Issue 2 | Apr - Jun - 2017***
ISSN Online: 2278-2656 ***Journal Home page: www.ijrpp.com***

Research article ***Open Access***

A comparative study of efficacy and safety of topical travoprost 0.004% versus latanoprost 0.005% in the treatment of primary open angle glaucoma at a tertiary care hospital

C R Jayanthi[1], Divyashree R N[2], Sujatha R[3]

[1]*Professor and HOD, 2 Post graduate, Department of Pharmacology*
[3]*Professor, Department of Ophthalmology, Minto Ophthalmic hospital, Bangalore Medical College & Research Institute, Bengaluru, Karnataka, India*

***Corresponding author: Divyashree R N**
Email: drdivyavinay@yahoo.co.in

ABSTRACT

Introduction

Glaucoma, "silent thief of sight" is a chronic, progressive optic neuropathy leading to optic nerve damage and visual field loss. Lowering intraocular pressure (IOP) in patients with primary open-angle glaucoma (POAG) is beneficial in reducing the risk for visual field loss in the long term. Various prostaglandin analogues have demonstrated consistent superiority over other therapies in terms of IOP reduction, however superiority amongst them remains inconclusive.

Objectives

To compare efficacy and safety of topical travoprost 0.004% versus latanoprost 0.005% in reducing intraocular pressure in patients with POAG.

Materials and methods

60 newly diagnosed patients of POAG who fulfilled the inclusion /exclusion criteria were randomised into two groups of 30 each to receive either travoprost or latanoprost once daily in the evening. Efficacy was measured in terms of reduction in IOP monitored at 4, 8 and 12 weeks from baseline. Safety was assessed by monitoring treatment emergent adverse drug reactions.

Results

Both travoprost and latanoprost effectively reduced IOP when compared to baseline. Mean IOP reduction from baseline to week 12 was 9.08 ± 1.93 mmHg (p<0.001), 7.96 ± 1.11 mmHg, (p<0.001) in travoprost and latanoprost groups respectively. There was significant reduction in IOP with travoprost when compared to latanoprost (8.86 ± 2.07 vs 7.71 ± 0.92, p=0.0003) at the end of 8 weeks and the same trend continued even at 12 weeks (9.08 ± 1.93 mmHg vs 7.96 ± 1.11 mmHg, p< 0.0002). Adverse drug reactions (ADR) were comparable in both the groups with conjunctival hyperaemia (21.6%) being the most common ADR.

Conclusion

Travoprost was found to be more efficacious in reducing IOP as early as 8 weeks as compared to latanoprost. There was an additional 1.12 mmHg reduction in IOP at the end of 12 weeks in comparison to latanoprost and it was well tolerated. Hence travoprost could be a favourable option for the treatment of primary open angle glaucoma.

Keywords: Latanoprost, Travoprost, Primary open angle glaucoma, Intraocular pressure

INTRODUCTION

Glaucoma is an optic neuropathy with characteristic damage to the optic nerve leading to visual field loss and irreversible blindness. [1] Around 60 million patients worldwide suffer from glaucoma and 12 million are in India, accounting for one fifth of the global burden. [2] Glaucoma is primarily classified as open-angle or closed-angle, depending on whether the drainage area for aqueous humor in the front of the eye has an open or closed appearance. POAG, with a mean prevalence of 1.96, primarily results from impaired or suboptimal drainage of aqueous humor out of the eye via the trabecular meshwork and/or uveoscleral pathways. [3] Lacking a clearly elucidated mechanism of disease to target therapeutically, treatment for glaucoma is aimed at risk factor modification. Of all the risk factors, IOP is the only modifiable risk factor shown to delay or prevent the development of glaucoma in eyes with ocular hypertension and to prevent progression of glaucoma in eyes with and without elevated IOP. [3] IOP reduction can be achieved by either topical or systemic medications, by various laser therapies, and by a number of incisional surgical techniques. With the advent of the prostaglandin analogues (PGAs), a paradigm shift in the treatment of glaucoma and ocular hypertension was realized. Owing to their superior IOP-lowering efficacy, minimal risk of ocular and systemic side effects, and convenient once daily dosing regimen, PGAs have rapidly become the first choice of drugs. [4]

Travoprost and latanoprost are the PGAs commonly preferred in the management of glaucoma. But, travoprost is a highly selective, potent prostaglandin F (FP) receptor agonist, equal or superior to latanoprost in lowering intraocular pressure, provides consistent diurnal IOP control, with significant IOP reductions persisting up to 84 hours post-dose. [3] Both the PGAs increase pulsatile ocular blood flow (pOBF) in the short term, but this effect will be kept constant only by travoprost. [5]

Considering the huge burden of glaucoma in India, paucity of Indian studies and the results of three meta-analysis remaining inconsistent with respect to superiority amongst various prostaglandin analogues, the above study was taken up.

MATERIALS AND METHODS

This was an open label, randomized prospective study conducted between May 2016-October 2016 in the Regional Institute of Ophthalmology, Minto Hospital attached to Bangalore Medical College and Research Institute, Bengaluru.

After obtaining institutional ethics committee clearance and written informed consent, the out-patients at the glaucoma clinic of either sex aged 18 years and above, newly diagnosed to be suffering from primary open angle glaucoma with mean (2 readings) IOP of $\geq$ 21mmHg at the baseline visit were enrolled in the study. Patients suffering from amblyopia, legal blindness (6/60 or less) in either eye, acute angle closure glaucoma, optic nerve disease, ocular infection or inflammation within the previous 3 months and anticipated use of topical or systemic steroids were excluded. Patients with severe trauma, any systemic contraindications or hypersensitivity to study medications were also excluded from the study.

A total of 60 patients were recruited and randomized in a 1:1 ratio into two groups of 30 each using computer generated randomization sequence (www.random.org/sequences) to receive 1 drop of either BAK (Benzalkonium chloride) preserved travoprost 0.004% or BAK preserved latanoprost 0.005% eye drops in the conjunctival sac of the affected eye(s) once daily in the evening. For decreased risk of systemic adverse reactions after instillation of the drug nasolacrimal occlusion in the form of gentle pressure application using a finger into the medial angle of eye was recommended.

Demographic data, ocular history, medical history, concomitant medications and details of general, systemic and ophthalmological examination were recorded in the study proforma at baseline visit

(visit 1). Follow-up was done at 4 weeks (visit 2), 8 weeks (visit 3) and 12 weeks (visit 4) after administering the study drugs. A deviation of ±2 days for first follow-up and ±1 week for subsequent follow-ups were allowed. At follow-up visits pulse rate, blood pressure, IOP, slit lamp examination findings and visual acuity were recorded. When both eyes fulfilled the eligibility criteria, both were regarded as study eyes and IOP was measured in each eye at the subsequent follow-up visits. IOP was measured with Goldmann's applanation tonometer and mean of 2 readings was taken at each of the visits. If any systemic medication with a known effect on IOP was deemed necessary for the patient, the patient was withdrawn from the study.Adverse drug reactions were recorded in CDSCO (Central Drugs Standard Control Organization) ADR reporting form and graded according to severity.

SAMPLE SIZE CALCULATION

Sample size was estimated as 57 subjects with a mean reduction in IOP of 6.1 mmHg and standard deviation of 1.8 with travoprost and mean reduction in IOP of 7.1 mmHg and standard deviation of 1.2 with latanoprost from previous studies. Alpha error was set at 5% and power of the study at 80%.For better computation of results a sample size of 60 was considered in the study.

STATISTICAL ANALYSIS

The data collected was tabulated and analyzed using mean and standard deviation. Continuous variables were compared within the group using repeated measures ANOVA and between the groups using unpaired t-test. Categorical data was expressed as percentages/proportions and Chi-square test was done to compare the categorical variables.Statistical significance was defined as a *p* value of <0.05.Analyses were performed using VassarStats.

RESULTS

78 subjects were screened for inclusion in the study of whom 60 subjects who met the inclusion criteria and gave written informed consent to participate in the study were enrolled in the study. There were no drop outs and all the 60 patients completed the study. The study flow is depicted in figure 1.

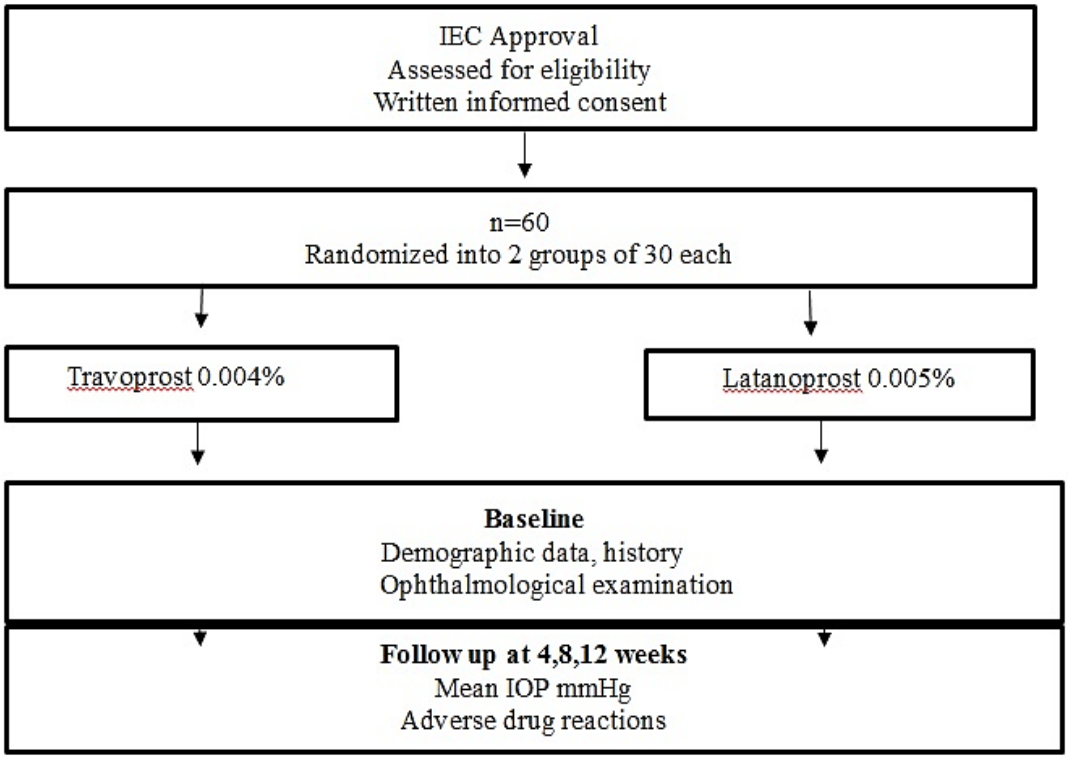


Figure 1: Flow chart of recruitment, randomization and follow up

DEMOGRAPHIC CHARACTERISTICS

Demographic profile of the patients included in the study is represented in Table 1. The study population in both the groups were matched with respect to baseline demographic characteristics.

Table 1: Demographic characteristics of the study population

Parameters	Group 1 Travoprost (n=30)	Group 2 Latanoprost (n=30)	*p* value
Age (Mean ± SD)	54.46 ± 10.85	55.2 ± 12.8	0.8*
18-40 years	04	05	
41-65 years	21	19	
≥ 66 years	05	06	
Gender			
Male	14 (46.7%)	13 (43.3%)	0.79**
Female	16 (53.3%)	17 (56.7%)	
Habits			
Smoking	04	05	0.75**
Alcohol	02	01	
Comorbidities			
Nil	18	15	
DM	06	07	0.60**
HTN	05	06	
DM + HTN	01	02	

* Data analysed using unpaired t test, **Data analysed using Chi-square, $p<0.05$ was taken as statistical significance
DM-Type 2 diabetes mellitus, HTN-Hypertension

MEAN REDUCTION IN IOP FROM BASELINE

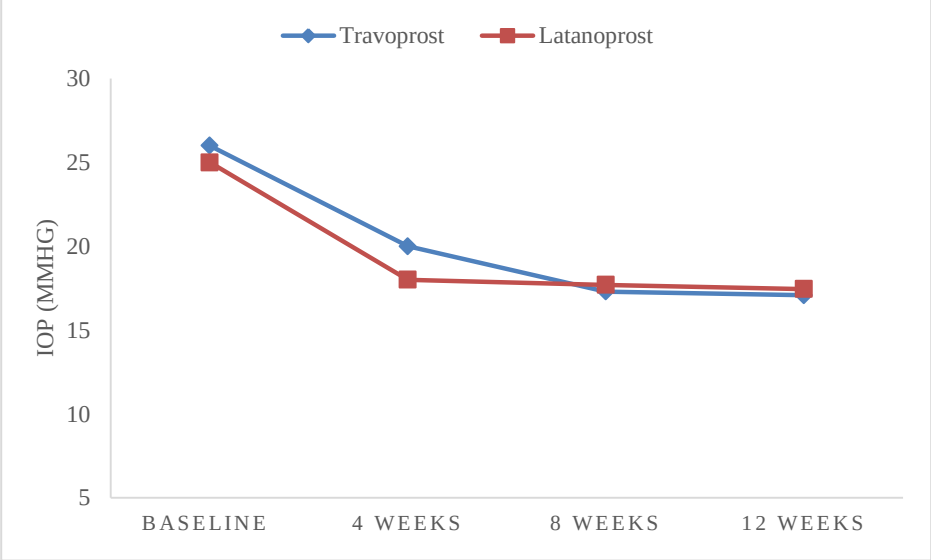
The baseline mean IOP in travoprost group was 26.16 ± 2.11 mmHg and 25.41 ± 3.14 mmHg in latanoprost group (p= 0.12). The mean intraocular pressure after 12 weeks of treatment was 17.08 ± 2.68 mmHg and 17.45 ± 2.02 mmHg in the travoprost group and in the latanoprost group respectively (Table 2, Graph 1). Both travoprost and latanoprost effectively reduced IOP at 12 weeks compared to baseline (p< 0.0001). IOP reduction at week 4 between the travoprost and latanoprost (6.7±2.98 vs 7.11±0.8, p=0.3) was not statistically significant. The reduction in IOP at week 8 and week 12 between travoprost and latanoprost was (8.86 ± 2.07 vs 7.71 ± 0.92, p=0.0003,) and (9.08 ± 1.93 mmHg vs 7.96 ± 1.11 mmHg, p< 0.0002, Graph 2) respectively from baseline. Travoprost in comparison to latanoprost significantly lowered IOP as early as 8 weeks which is of clinical importance in the management of POAG.

Table 2: Mean IOP at each visit in travoprost and latanoprost groups

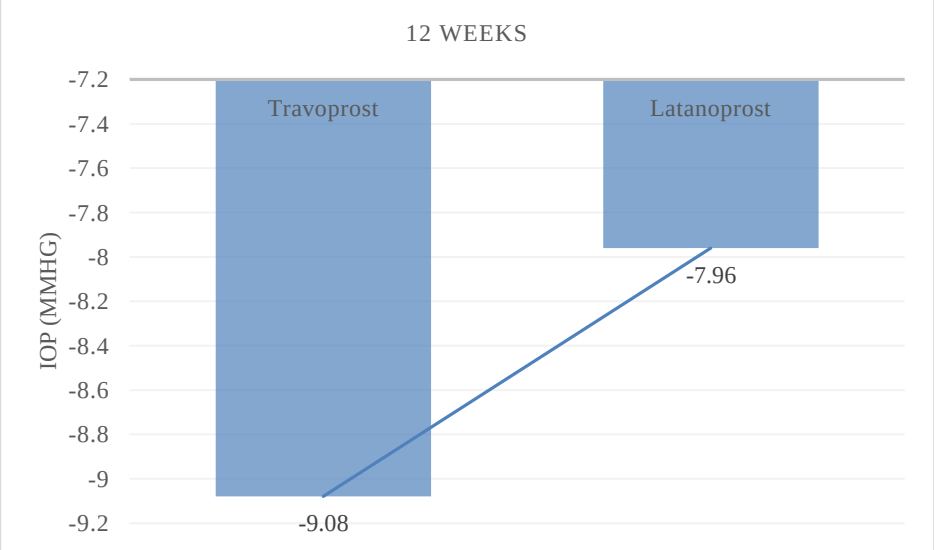
Group n=30 in each group	Baseline (mmHg)	Week 4 (mmHg)	Week 8 (mmHg)	Week 12 (mmHg)	*p* value
Travoprost (Mean ± SD)	26.16 ± 2.11	20.05± 2.49	17.3± 2.49	17.08 ± 2.68	< 0.0001*$
Latanoprost (Mean ± SD)	25.41 ± 3.14	18.3± 2.33	17.7 ± 2.21	17.45± 2.02	< 0.0001*$
***p* value –intergroup comparison at each follow up visit**	0.12†	0.3†	0.0003†#	0.0002†#	

*-Data analysed using repeated measures ANOVA, $- statistically significant
†- Data analysed using unpaired test, # statistically significant

Graph 1: Temporal depiction of mean IOP in the study groups



Graph 2: Reduction in IOP at 12 weeks from baseline



p- 0.0002 (unpaired t test)

The percentage reduction in IOP at the end of 12 weeks was 34.7% in the travoprost group and 31.3% in the latanoprost group.

Adverse drug reactions

Both the treatments in the study were well tolerated. The adverse drug reactions encountered were minor and there was no significant difference between the groups (c2 = 0.05, df = 1, *p* = 0.82) (Table 3).

Table 3: Adverse drug reactions

Adverse drug reactions	Travoprost No. of patients (%)	Latanoprost No. of patients (%)
Conjunctival hyperaemia	04 (6.7%)	05 (8.3%)
Burning sensation	02 (3.3%)	03 (5%)
Dry eye	04 (6.7%)	03 (5%)
Itching	02 (3.3%)	02 (3.3%)

DISCUSSION

Glaucoma is typically diagnosed by the presence of the "classical triad": characteristic pattern of visual field defects, optic neuropathy, normal or elevated intra-ocular pressure. The goal of management is to slow disease progression sufficiently to preserve lifelong vision while incurring few side effects. Prostaglandin analogues are the first-line drugs in glaucoma therapy. Although there is extensive evidence on the efficacy of the individual prostaglandin drugs, data determining the comparative effectiveness of the travoprost versus latanoprost are sparse and hence above study was taken up.

In the present study, the mean age was 54.46 ± 10.85 years in the travoprost group and 55.2 ± 12.8 years in the latanoprost group with no statistically significant difference between groups. These results correlate with a number of epidemiological studies which have shown an increase in incidence of glaucoma after age 40 with risk continuing to escalate with each additional decade. [6, 7, 8]

There were a total of 29 men and 31 women among the study population with no statistically significant difference in their distribution between groups which harmonises with a review of literature done by Vajaranant T S et al., which concluded that there is no clear gender predilection for POAG. [9]

Hypertension and diabetes mellitus are the most common systemic diseases seen in glaucoma subjects which was balanced between both the groups. Of the 60 patients enrolled in the study 13 (21%) of them were diabetic, 11 (18.3%) were hypertensives and 03 (5%) subjects had both diabetes and hypertension. The above findings diverge from a study by Dave A et al., wherein the incidence of hypertension, diabetes and both were 47.5%, 29.4% and 15.8% respectively which could be because of large sample size included in there study. [10] There were 09 (15%) smokers and 03 (5%) alcoholics among the 60 subjects in this study. Smoking and alcohol consumption have been identified as risk factors for the development of POAG, but their association with glaucoma is still controversial. [11], [12]

Elevated intraocular pressure is an important risk factor for glaucoma. Several recent studies support the concept of lowering IOP in glaucoma patients and suspects. [13, 14. 15, 16] It has been shown that every 1mmHg reduction in IOP reduces the relative risk of progression of glaucoma by 10%. Of all current therapies utilized in the treatment of POAG, PGAs demonstrate consistent superiority over beta-adrenergic blockers, alpha-adrenergic agonists or topical carbonic anhydrase inhibitor therapies as far as IOP-lowering efficacy is concerned. PGAs, lower IOP by increasing the uveoscleral outflow of aqueous humor. Clinically used PGAs bind to PGF receptors and this FP-receptor binding by prostaglandin F2α and its analogues results in numerous physiologic responses within ciliary muscle cells. These include phosphoinositide turnover, intracellular Ca2+ mobilization, and mitogen-activated protein (MAP) kinase activation. [17] The results of these FP receptor-mediated intracellular signals include increased production of several matrix metalloproteinases (MMPs), specifically MMP-1, -2, -3 and-9, in human ciliary smooth muscle cells. Remodelling of the extracellular matrix of the ciliary body is hypothesized to lower IOP by creating or increasing spaces between the ciliary muscle fibre bundles, thus increasing outflow through the uveoscleral pathway. [18, 19, 20, 21]

Primary objective of the study was evaluating the efficacy of two PGAs namely travoprost and latanoprost. The present study showed that travoprost reduced IOP significantly as early as 8 weeks when compared to latanoprost and it was well sustained at the end of 12 weeks which could be beneficial in patients with glaucoma.

Comparable outcomes were noted in a phase III study by Netland P A et al., where travoprost was significantly better than latanoprost in lowering IOP. Travoprost lowered IOP by a statistically significant

0.8 mmHg more than latanoprost. [22] In a multicentre, randomized, double masked, active-controlled, parallel-group trial conducted by Eugenio Maul et al., there was a statistically significant difference in reductions from baseline in pooled IOP during the masked phase of the study between the travoprost and latanoprost groups. [23] In a study by Sawada A et al., travoprost had similar effect as latanoprost in reducing the IOP in glaucoma patients. [24] The Parrish study shows equivalent efficacy among the prostaglandin analogues. [25] The findings from the meta-analysis of 17 RCTs by Jin-Wei Cheng et al. suggest that there were no significant differences between travoprost and latanoprost in IOP reduction in patients with POAG. [26]

The percentage reduction of IOP with travoprost and latanoprost was 34.7% and 31.3 % respectively. All of the Prostaglandin analogues (PGA) have been shown to reduce IOP from baseline values by ≥30%. PGAs like latanoprost (0.005%), or travoprost (0.004%) are preferable if the target is to achieve 30-35% IOP reduction from the baseline.

The secondary objective that was assessed in the study was the safety of the two study medications. The conjunctival hyperaemia was the commonest ocular adverse drug reaction (15%) shadowed by dry eye (11.7%), burning sensation (8.3%) and itching (6.6%). The percentage of patients with hyperaemia travoprost group was 6.7% and in latanoprost group was 8.3%. The adverse drug reactions encountered were minor ocular adverse drug reactions and there was no statistically significant difference between the groups (p=0.82). Neither serious adverse drug reactions nor systemic side effects were observed with both the study medications. Both were well tolerated. Similar results were obtained from meta-analysis by Jin-Wei Cheng et al., with respect to safety and tolerability of prostaglandin analogues. [26]

Prostaglandins are currently the most effective topical medications for decreasing IOP, an important and easily measured intermediate outcome on the path to vision loss. Excellent safety and efficacy of PGAs and round the clock control of IOP has provided a cutting edge over other ocular hypertensives. To the best of our knowledge the current study is probably the first of its kind which evaluated the role of PGAs amongst Indian patients, and randomization of the study subjects added to the strength of the study. The study had few limitations: it was an open label study, the effect of IOP reduction on the progression of visual field loss on long term was not assessed as the subjects were followed up only for a short duration i.e 3 months and the effect of the study drugs on diurnal variations in IOP was not evaluated in the study.

CONCLUSION

The prostaglandin analogue travoprost 0.004% contributed an additional 1.12 mmHg reduction in IOP at end of 12 weeks and the reduction in IOP was statistically significant as early as 8 weeks compared to latanoprost and was well tolerated. Hence travoprost could be a favourable option for the treatment of primary open angle glaucoma.

"DON'T LOSE SIGHT TO GLAUCOMA"

ACKNOWLEDGEMENTS

We would like to thank the patients who participated in this study and also faculty of Department of Ophthalmology, Minto Ophthalmic hospital, and faculty of Department of Pharmacology Bangalore Medical College & Research Institute, Bengaluru for their extended support and immense help in this project.

SOURCE OF FUNDING: Nil

POTENTIAL CONFLICT OF INTEREST: Nil

REFERENCES

[1]. Sihota R, Tandon R. The Glaucomas. In: Sihota R, Tandon R, editors. Parson's Diseases of the eye. Noida: Elsevier, 21, 2011, 280-300.

[2]. Saxena R, Singh D, Vashist P. Glaucoma: An Emerging Peril. Indian Journal of Community Medicine : Official Publication of Indian Association of Preventive & Social Medicine. 38(3), 2013, 135-137. doi:10.4103/0970-0218.116348.

[3]. Denis P, Covert D, Realini A. Travoprost in the management of open-angle glaucoma and ocular hypertension. Clinical ophthalmology. 1(1), 2007, 11-24.

[4]. Jill Autry, Elyse Chaglasian. Glaucoma and the New Prostaglandins. Review of cornea and contact lenses. 2012. Available at: http://*www.reviewofcontactlenses.com/content/d/down_on_the.../34139/*

[5]. Cardascia N, Vetrugno M, Trabucco T, Cantatore F, Sborgia C. Effects of travoprost eye drops on intraocular pressure and pulsatile ocular blood flow: a 180-day, randomized, double-masked comparison with latanoprost eye drops in patients with open-angle glaucoma. Curr Ther Res Clin Exp. 64(7), 2003, 389–400. doi: 10.1016/S0011- 393 X (03)00112-7.

[6]. Varma R, Lee PP, Goldberg I, Kotak S. An Assessment of the Health and Economic Burdens of Glaucoma. American journal of ophthalmology. 152(4), 2011, 515-522. doi:10.1016/j.ajo.2011.06.004

[7]. Klein BE, Klein R, Sponsel WE, Franke T, Cantor LB, Martone J et al. Prevalence of glaucoma. The Beaver Dam Eye Study. Ophthalmology. 99(10), 1992, 1499-504.

[8]. Leske MC, Wu SY, Honkanen R, Nemesure B, Schachat A, Hyman L, et al. Nine-year incidence of open-angle glaucoma in the Barbados Eye Studies. Ophthalmology. 114(6), 2007, 1058–1064

[9]. Vajaranant TS, Nayak S, Wilensky JT, Joslin CE. Gender and glaucoma: what we know and what we need to know. Current opinion in ophthalmology. 21(2), 2010, 91-99. doi:10.1097/ICU.0b013e3283360b7e.

[10]. Dave A, Bali SJ, Sharma R, Khurana AK, Gupta R, Dada Prevalence of diabetes mellitus and hypertension among Indian glaucoma patients and evaluation of systemic therapy. TInt Ophthalmol. 33(5), 2013, 527-32.doi: 10.1007/s10792-013-9737-3.

[11]. Wise LA, Rosenberg L, Radin RG, Mattox C, Yang EB, Palmer JR, et al. A prospective study of diabetes, lifestyle factors, and glaucoma among African-American women. Ann Epidemiol. 21, 2011, 430-9

[12]. Fan BJ, Leung YF, Wang N, Lam SC, Liu Y, Tam OS, et al. Genetic and environmental risk factors for primary open-angle glaucoma. Chin Med J. 117, 2004, 706–10.

[13]. The advanced glaucoma intervention study (AGIS): 7. the relationship between control of intraocular pressure and visual field deterioration .American Journal of Ophthalmology , 130(4), 429 - 440

[14]. Musch DC, Lichter PR, Guire KE, Standardi CL. The Collaborative Initial Glaucoma Treatment Study: study design, methods, and baseline characteristics of enrolled patients. Ophthalmology.106(4), 1999, 653-62

[15]. Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP, Parrish RK 2nd, Wilson MR, Gordon MO. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 120(6), 2002, 701-13; discussion 829-30.

[16]. Leske MC, Heij A, Hyman L, Bengtsson B. Ophthalmology. Early Manifest Glaucoma Trial: design and baseline data.106(11), 1999, 2144-53

[17]. Kelly CR, Williams GW, Sharif NA.Real-time intracellular Ca2+ mobilization by travoprost acid, bimatoprost, unoprostone, and other analogs via endogenous mouse, rat, and cloned human FP prostaglandin receptors. J Pharmacol Exp Ther. 304, 2003, 238–45.

[18]. Yousufzai SY, Ye Z, Abdel-Latif AA. Prostaglandin F2 alpha and its analogs induce release of endogenous prostaglandins in iris and ciliary muscles isolated from cat and other mammalian species. Exp Eye Res. 63(3), 1996, 305-10

[19]. Zhan GL, Camras CB, Opere C, Tang L, Ohia SE. Effect of prostaglandins on cyclic AMP production in cultured human ciliary muscle cells. J Ocul Pharmacol Ther. 14(1), 1998, 45-55.

[20]. Lindsey JD, Kashiwagi K, Kashiwagi F, et al. Prostaglandins alter extracellular matrix adjacent to human ciliary muscle cells in vitro. Invest Ophthalmol Vis Sci, 38, 1997, 2214–23.

[21]. Schachtschabel U, Lindsey JD, Weinreb RN. The mechanism of action of prostaglandins on uveoscleral outflow. Curr Opin Ophthalmol, 11, 2000, 112–15.

[22]. Netland P A, Landry T, Sullivan E K, Andrew R, Silver L, Weiner A, et al. Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. Am J Ophthalmol . 132 (4), 2001, 472-84.

[23]. Maul E, Carrasco FG, Costa VP, Casiraghi JF, Vargas E, Sarmina JS, Mayol R.A 6-week, multicenter, randomized, double-masked, parallel-group study comparing travoprost 0.004% to latanoprost 0.005% followed by 6-week, open-label treatment with travoprost 0.004%.Clin Ther. 29(9), 2007, 1915-23.

[24]. Sawada A, Yamamoto T, Takatsuka N. Randomized crossover study of latanoprost and travoprost in eyes with open-angle glaucoma. Graefes Arch Clin Exp Ophthalmol. 250(1), 2012, 123-9. doi: 10.1007/s00417-011-1762-1

[25]. Parrish RK, Palmberg P, Sheu WP.A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: a 12-week, randomized, masked-evaluator multicenter study. Am J Ophthalmol, 135, 2003, 688–703.

[26]. Cheng JW, Xi JL, Wei RL, Cai JP, Li Y. Effects of travoprost in the open angle glaucoma or ocular hypertension: A systematic review and meta-analysis. Current therapeutic research. 70(4), 2009, 335–350.doi:10.1016/j.curtheres.2009.08.006.