Original Article

A Comparison 24 Hour Intraocular Pressures Between Travoprost 0.004% and Timolol Gel 0.1% on Controlled Primary Open Angle Glaucoma

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ABSTRACT

Background: *To compare 24 hours intraocular pressure (IOP) in patients controlled primary open angle glaucoma treated with timolol gel 0.1% versus travoprost 0.004%.*

Method: *26 controlled primary open angle glaucoma patients were randomized to received travoprost 0.004% dosed in the evening or timolol gel 0.1% dosed in the morning. After 4 weeks of treatments 24 hours IOP curved was performed at 9 a.m until 6 a.m every 3 hours.*

Result: *The mean IOP of travoprost 0.004% group was 12.2±1.5 mmHg and timolol 0.1% group was 13.4±1.9 mmHg ($p>0.05$). The IOP fluctuation of travoprost 0.004% was 3.9±1.4 mmHg and timolol gel 0.1% was 5.9±1.4 mmHg ($p<0.05$). Peak IOP travoprost 0.004% was 14.3±1.7 mmHg and timolol gel 0.1 % was 16.8±1.7 mmHg ($p<0.05$). Travoprost 0.004% has lower IOP in almost each point measurement compare to timolol gel 0.1%.*

Conclusion: *Travoprost 0.004% has lower fluctuation, peak and mean IOP compare to timolol gel 0.1%.*

Keywords: *Primary open angle glaucoma, IOP fluctuation, peak IOP, travoprost 0.004%, timolol gel 0.1%*

Glaucoma is the second largest causes of blindness after cataract in the world according to WHO in 2002. Patients with glaucoma is estimated to reach 60.5 milions and increased to 70.9 milions in 2020. It was estimated that in 2010, 4.5 million people will be blind and increased to 5.9 million in 2020 due to open angle glaucoma (OAG).[1-4] Faiqoh[5] reported 650 new OAG patients who came for treatment during the period 2001-2010 in Cipto Mangunkusumo hospital and was the highest form of glaucoma after secondary glaucoma.[1,2,4] Glaucoma progression is determined by several risk factors. Intraocular pressure is the only factor that can be modified to inhibit glaucoma progression.[2,3,6-10] Studies showed that glaucoma patients with controlled IOP still have glaucoma progression. Fluctuations, mean, and peak IOP is a factor that contributes to progression of glaucoma. Advance Glaucoma Intervention Study (AGIS)[11] reported that long term IOP fluctuations play role in the progression of glaucoma. Asrani etal[12] showed that diurnal IOP fluctuations as risk factor for progression of glaucoma. Stewart et al[13] showed that low IOP fluctuations is an important factor in prevention of progression in advanced glaucoma. The goal of

glaucoma treatment in open angle glaucoma is to inhibit progression by lowering IOP to reach target pressure using medical, laser or surgical. Currently available classes of drugs are considered effective to lower average IOP but have limited data on the effects of fluctuations and peak IOP. Travoprost 0.004% and timolol gel 0.1% was two first line regimen drugs that can be given to primary OAG (POAG).

Several previous studies have compared the effectiveness of travoprost and timolol therapy. Fellman et al[14] showed travoprost provided lower mean IOP than timolol. Konstas[15] conducted a study on fluctuations with the result of IOP fluctuations using travoprost was 3.2±1.0 – 4.0±1.5 mmHg. Metaanalysis by Stewart et al[16] of 24 hour IOP fluctuations showed that the range of IOP fluctuation for timolol was 4.4±1.8 – 7.0±3.2mmHg. Until now there was no study that showed comparison IOP fluctuations in patients with contolled IOP treated with travoprost or timolol gel. The purpose of this study was to compare the IOP for 24 hours in controlled POAG patients who received travoprost 0.004% with timolol gel 0.1%.

MATERIAL AND METHOD

Patients

Designs of this study were prospective, cross-sectional, single blind clinical trial. Patients were recruited from glaucoma division of Cipto Mangunkusumo hospital. All patients who agreed to participated in this study and met inclusion criteria and exclusion criteria were consecutively enrolled. The eye included in this study was the eye with the lowest IOP, if the IOP were equal, the right eye was chosen. Patients with a previous history of glaucoma surgery, laser, LASIK, corneal abnormality, pregnant or nursing women, on corticosteroid or beta blocker treatment or any medication that may affect IOP were excluded.

Method

Informed consent was signed. This study protocol was approved by the Health Research Ethics Commite Faculty of Medicine Universitas Indonesia. Patients who met criteria were divided to 2 group randomly assigned to received treatment with travoprost 0.004% (Travatan 0.004%, Alcon Lab Inc.) or timolol gel 0.1% (Timol Gel 0.1%, Cendo).

For the purpose of masking, patients have been relabeled and put in the same box. On the first visit, visual acuity, IOP, slit lamp examination and central corneal thikcness was performed. After 4 weeks of therapy patients were re-examined, patients with IOP >21mmHg were excluded. Patients with IOP <21mmHg will stay in guest house for 24 hours IOP examination which were performed 8 times from 9 a.m until 6 a.m next day with 3 hours interval, using PERKINS tonometer by one examiner.

Statistic

Statistical analysis was performed using SPSS version 11. Qualitative variables were stated using percentage, and quantitative variables were stated using mean (standard deviation SD). Statistical differences between therapy were assessed using the independent T-test or Mann Whitney u test.

Primary efficacy parameter was fluctuation IOP between treatments. This study had 90% power for identifying fluctuation in IOP of 1.5 mmHg differences between treatments assuming SD 2.5 mmHg. The significance level was set 5% and 2 way analysis was used.

RESULT

A total of 26 patients were included this study with 9 female and 17 male. All patients had controlled POAG. The mean ± SD age for the travoprost 0.004% and timolol gel 0.1% group was 66.2±10.7 and 65.9±6.2 respectively. Other demographic comparison was show on Table 1.

Table 1. Data Characteristic

Subject Characteristic	Travoprost	Timolol Gel	p
Gender*			
Female	4	5	1.00
Male	9	8	
Age			
<70 y.o	7	9	0.68
≥70 y.o	6	4	
Lens status			
Phakic	6	5	1.00
Pseudophakic	7	8	
Type previous treatment*			
Beta-blocker	9	9	1.00
Prostaglandin	4	4	
Previous treatment period*			
<1 year	11	11	1.00
≥1 year	2	2	

*Fisher test

Table 2. Demographic Data

Variable	Travoprost	Timolol Gel	p
	Mean ± SD	Mean ± SD	
Subject age	66.2±10.7	65.9±6.2	0.947
Systolic pressure	139.4±2.3	139.0±0.9	0.964
Diastolic pressure	80.4±14.8	77.4±15.1	0.614
Pulse	79.7±14.4	73.5±1.1	0.233
Baseline IOP	14.8±2.2	15.6±2.2	0.339
Corneal thickness	522.1±26.5	541.5±32.7	0.401

24 Hour Intraocular Pressure

The 24 hours mean IOP are shown in figure 1. Travoprost group has lower IOP compared to timolol gel group in each point measurement. IOP mean difference significanly occured at 3, 6, 9, 12.

Table 3. Distribution of peak IOP subjects based on study group

Variable: Peak IOP	Travoprost n=13 (%)	Timolol Gel n=13 (%)	p
≤18 mmHg	13 (100)	9 (69.2)	0.09*
>18 mmHg	0 (0)	4 (30.8)	

*Uji Fisher

Table 4. Distribution of IOP fluctuation subjects based on study group

Variable: IOP Fluct	Travoprost n=13 (%)	Timolol Gel n=13 (%)	p
≤3 mmHg	4 (30.8)	0 (0)	0.09*
>3 mmHg	9 (69.2)	13 (100)	

*Uji Fisher

DISCUSSION

IOP reduction is still the only way to prevent the occurence of progression in patients with glaucoma. The Early Manifest Glaucoma Trial[6] showed that every increase in 1 mmHg IOP will increases the risk progression by 10%. Some studies suggest that there are other factors suspected to affect the progression of glaucoma-related eye pressure include IOP fluctuation and peak IOP.[12,19,27,38-41]

IOP fluctuation is one of independent risk factors that may increase the progression of glaucoma. Progressive visual field damage in eyes with controlled IOP is suspected as a result of fluctuation IOP over 24 hours. IOP during 24 hours examination is the gold standart to determine IOP fluctuation.

Table 5. Mean/median IOP variable

Variable	Travoprost	Timolol Gel	p
	Mean ± SD	Mean ± SD	
Minimum IOP	10.0 (10.0–13.0)	10.0 (8.0–15.0)	0.88
Peak IOP	14.3±1.7	16.8±1.7	0.001
Mean IOP	12.2±1.5	13.4±1.9	0.07
IOP fluctuation	3.9±1.4	5.9 ±1.4	0.001
IOP on clinical hour	12.0±1.4	14.2±1.8	0.002
IOP outside clinical hour	12.2±1.5	12.7±2.2	0.53

Some authors get different result on the risk of progression of glaucoma due to IOP fluctuation. Nouri et al[19] concluded in his study that an increase in the risk of progression by 30% to an increase of 1 mmHg IOP fluctuation. Lee et al[42] conducted a study involving patients primary open angle glaucoma, low pressure glaucoma and ocular hypertension get results in his study that every 1 mmHg increase in fluctuations can increase five fold progression for five years in intraocular pressure controlled.

This study reports the results of IOP over 24 hours in patients who have undergone therapy with travoprost 0.004% and timolol gel 0.1%. IOP fluctuations in the travoprost group was 3.9 mmHg while on on timolol gel group was 5.9 mmHg, there was a statisticaly significant difference between the two groups. These result are consistent with several studies regarding IOP fluctuation in the travoprost therapy has been done before where administration travoprost IOP fluctuations varies with the range of 3.2-4.0 mmHg. Nomura et al[43] showed IOP fluctuation by 3.9 mmHg in normo tension glaucoma patient who received travoprost at evening.

Travoprost administration in this study was given in the evening at 8 PM. Travoprost administration in evening showed better result in lowering IOP fluctuation. Lower IOP fluctuation during 24 hours at travoprost group compared with timolol group may be caused by differences in drugs way and duration of action.[33, 34, 44, 45]

Timolol administration in this study was given in 8 AM. In this study IOP fluctuation in the timolol group was 5.9 mmHg. IOP fluctuations in patients treated with timolol gel provide different results with a range of 4.4-7.0 mmHg. Larsson et al[46] showed IOP fluctuation by 5.3 mmHg in patients with glaucoma and ocular

hypertension treated with timolol gel. Konstas et al [47]obtain IOP fluctuations in patients treated with timolol gel 0.5% by 5.6 mmHg.

In this study there were 4 subjects in the travoprost group had IOP fluctuation ≤3 mmHg, whereas all subject in the timolol group has IOP fluctuation >3 mmHg. Nouri et al[19] showed that IOP fluctuation >3 mmHg is one factor that can lead to long term progression in glaucoma patient who have recived therapy.

In this study, mean IOP for 24 hours in the travoprost group amounted to 12.2±1.4 mmHg while on timolol gel group was 13.4±1.9 mmHg, but this difference was not statisticaly significant. Orzalesi et al[48] showed the mean 24 hours IOP in patients receiving timolol was 18.5±1.2 mmHg and 16.8±0.9 mmHg in patients treated with latanoprost. Konstas et al [15] showed the mean 24 hours IOP in glaucama patients given travoprost was 17.3±1.9 mmHg. These result showed that the mean IOP by both group as well as a group of timolol gel and travoprost have same effectiveness in maintaining IOP remained low during for 24 hours. This is because the subjects in this study were glaucoma patients with controlled IOP who have previously. Travaprost group had a mean IOP lower in every point of the examination when compared with timolol gel group. Travoprost group has mean IOP lower in every point of examination if compared to timolol group; it's statistically significant in 6, 9, and 12 a.m. This is most likely caused by tavoprost better effect in lowering IOP these hours. This study had mean IOP results were lower when compared to previous studies this is likely due to the fewer number of samples. Study conducted by advance AGIS concluded that all patients with glaucoma with a mean IOP <18 mmHg showed no progression over 6 years.[11]

The mean peak IOP in the travoprost group was 14.3±1.7mmHg while the mean peak IOP on timolol group was 16.8±1.7mmHg. The results in this study indicate that although travoprost group and timolol group had the same mean peak IOP less than 18 mmHg, but timolol group there were 4 subjects with peak IOP ≥18mmHg. The mean peak IOP ≥ 18 mmHg is one risk factor for progression to glaucoma patients with controlled IOP. Several studies suggest the peak IOP ≤18mmHg. [25,49]

In this study the 11 subjects out of 26 subjects had a peak IOP occured after clinic hours, four subject of travoprost group and seven subjects of timolol group. These results are consistents with previous study conducted by Konstas et al[47] which showed that 50% of patients who received therapy IOP peaks may occur after clinic hours. Peak iop in patients with glaucoma may accur at any time. Wilensky et al[50] conducted the study with measurements over 24 hours in glaucoma patients with controlled IOP and showed that 50% of patients obtained peak IOP occured after clinic hours. 24 hours IOP measurement is a measurement of physiological IOP to be able to know the peak and IOP fluctuation. Some authors try to modify IOP measurements to asses the peak and IOP fluctuation by water drinking test. however, it has limitations in glaucoma patients who have cardiovascular abnormalitiesthat often occur in elderly.

This study has limitations, include, repeated measurements made at middle of the night can disrupt sleep patterns of patients that can affect a patient's circadian rhythm. This study did not have 24 hours IOP before the start of therapy and therefore we can not know the magnitude of IOP lowering effect to treatment. This study showed that fluctuations, peak, and mean 24 hours IOP in travoprost group better than timolol gel group in controlled primary open angle glaucoma.

REFERENCES

1. Quigley H A, Broman A T. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmo. 2006;90:262-7.
2. Staff AAO. Glaucoma Basic and clinical science. San Fransisco; 2009-2010.
3. Kooner K.S. Clinical Pathways in Glaucoma. New York: Thieme New York; 2001.
3. Cook C, Foster P. Epidemiology of glaucoma whats new? Can J opthalmol. 2012;47:223-6.
4. Faiqoh M. Karakteristik pasien di divisi glaukoma poliklinik mata rscm tahun 2001-2010 Jakarta: universitas Indonesia; 2011
5. Leske M.C, Heijl A, Hussein M, Hyman L, Bengtsson B, komarof E. Factors for Glaucoma progression and the effect of treatment. The Early Manifest Glaucoma Trial. Arch Ophthalmol. 2003;121:48-56.
6. Chiselita D, Motoc I, Danielescu C. Daily and nightly fluctuation of intraocular pressure and blood pressure in glaucoma and non glaucoma patients. Oftalmologia. 2008;52:119-25.

7. Sihota R, Saxena R, Gogoi M, Sood A, Gulati V, Pandey M. A comparison of the circadian rhythm of intraocular pressure in primary chronic angle closure glaucoma, primary open angle glaucoma and normal eyes. Indian J Ophthalmol 2005;53:243-7.
8. Bello C M, Chauhan B C, NIicolela M T, Mccormick T A, Leblanc R. Intraocular Pressure and Progression of Glaucomatous Visual Field Loss. Am J Ophthalmol. 2000;129:302-8.
9. Rivera J L, Bell N P, Feldman R M. Risk factors for primary open angle glaucoma progression: what we know and what we need to know. Current Opinion in Ophthalmology. 2008;19:102-6.
10. AGIS I. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol 2000;130:429-40.
11. Asrani S, Zeimer R, Wilensky J, Gieser D. Large diurnal fluctuations in intraocular pressure are independent risk factor in patients with glaucoma. J Glaucoma. 2000;9:134-42.
12. Stewart WC CR, Hunt HH, . Factors associated with visual field loss in patients with advanced glaucomatous changes in the optic nerve head. Am J Ophthalmol. 1993;116:176-81.
13. Fellman RL SK, Ratlif M, Silver HL, Whitson JT. Comparison of Travoprost 0.0015% and 0.004% with Timolol 0.5% in Patients with Elevated Intraocular Pressure. Ophthalmology 2002;109:998-1008.
14. Konstas A.G.P, Mikropoulos D.G, Kaltsos K, Stewart W.C. 24-Hour Intraocular Pressure Control Obtained with Evening- versus Morning-Dosed Travoprost in Primary Open-Angle Glaucoma. Ophthalmology. 2006;113:446-50.
15. Stewart WC KA, Kruft B, Heather MM, Stewart JA. Meta-Analysis of 24-h Intraocular Pressure Fluctuation Studies and the Efficacy of Glaucoma Medicines. J Ocul pharmacol and ther. 2010;26:175-80.
16. Tamm E.R, Toris C, Crowston J, Sit A, Lim S, Lambrou G,. Basic science of intraocular pressure Amsterdam: Kugler Publications; 2007
17. Stampers R.L, Lieberman M.F, Drake M.V. Aqueous humor formation in Beckers shafers diagnosis and therapy of the glaucomas. 8 ed. china: Elsevier Inc.; 2009.
18. Nouri-Mahdavi K HD, Coleman A. Predictive factors for glaucomatous visual field progression in advanced glaucoma intervention study. ophthalmology. 2004;111:1627-35.
19. David R, Zangwill L, Briscoe D, Dagan M, Yagev R, Yassur Y. Diurnal intraocular pressure variations: an analysis of 690 diurnal curves. British Journal of Ophthalmology 1992;76:280-3.
20. Bagga H, John H.K. Liu J.H.K, Weinreb R.N. Intraocular pressure measurements throughout the 24 h. Curr Opin Ophthalmol. 2009;20:79-83.
21. Hara T, Hara T, Tsuru T. Increase of Peak Intraocular Pressure During Sleep in Reproduced Diurnal Changes by Posture. Arch Ophthalmol. 2006;124:165-8.
22. Doshi AB LJ, Weinreb RN. Circardian change in intraocular pressure. Berlin: Springer-Verlag; 2009.
23. Barkana Y AS, Liebmann J, Tello C, Robert Ritch R. Clinical utility of intraocular pressure monitoring outside of normal office hours in patients with glaucoma. Arch Ophthalmol. 2006;124:793-7.
24. De Moraes C.G.V, Juthani V.J, Liebmann J.M, Teng C.C, Tello C, Susanna Jr R, Ritch R. Risk Factors for Visual Field Progression in Treated Glaucoma. Arch Ophthalmol 2011;129:562-8.
25. Kenneth Schwartza K, Budenzb D. Current management of glaucoma. Curr Opin Ophthalmol. 2004;15:119-26.
26. Leske M.C, Heijl A, Hyman L, Bengtsson B, Dong L, Yang Z,. Predictors of long-term progression in the early manifest glaucoma trial. Ophthalmology 2007;114:1965-72.
27. Khouri A.S, Lama P.J, Fecthner R.D. Glaucoma medical therapy principles and management. new york: Oxford university press; 2008.
28. Zimmermant T.J, Bauman J.D, Hetherington J, . Side effects of timolol. Surv of ophthalmology. 1983;28 243-9.
29. Chiang, Ho J I, Chen J.C. Pharmacokinetics and intraocular pressure lowering effect of timolol preparations in rabbit eyes. Journal of ocular pharmacology and therapeutics 1996;12:471-80.
30. Dickstein K, Aarsland T. Comparison of the effects of aqueous and gellan ophthalmic timolol on peak exercise performance in middle aged men. Am J Ophthalmol 1996;121:367-71.
31. Hellberg MR, Verney L, Salle VL, Mclaughlin MA,. Sharif NA, Desantis L, Dean TR,. Zinke PW. Preclinical efficacy of Travoprost, a potent and selective FP prostaglandin receptor agonist. J Ocul pharmacol and ther 2001;17.
32. Toris CB, Zhan G, Fan S, Dickerson JE, Landry TA, Bergamini MV, Camras CB. Effects of Travoprost on Aqueous Humor Dynamics in Patients With Elevated Intraocular Pressure. J Glaucoma. 2007;16:189-95.
33. Toris CB. Update on the mechanism of action of topical prostaglandins for intraocular pressure reduction. Surv Ophthalmol 2008;53:107-20.
34. Netland PA. Travoprost Study Group: Response to travoprost in black and non black patients with open angle glaucoma or ocular hypertension. Adv Ther. 2003;20:149-63.
35. Goldberg I, Cunha-Vaz JC, Jakobsen JE, Nordmann JP, Trost E, Sullivan K. Comparison of topical Travoprost eye drops given once daily and timolol 0.5% given twice daily in patients with open-angle glaucoma or ocular hypertension. Journal of Glaucoma. 2001;10:414-22.
36. Stewart WC, Stewart JA, Nelson LA, Kruft B. Mean Standart Deviation for common glaucoma treatments. Acta Ophthalmol. 2009;87(1):112-4.
37. Lichter PR. Expectations from clinical trials results of the early manifest glaucoma trial. Arch Ophthalmol 2002;120:1371-2.
38. Martinez-Bello C CB, Nicolela MT. Intraocular pressure and progression of glaucomatous visual field loss. Am J Ophthalmol. 2000;129:302-8.
39. Medeiros F.A WRA, Zangwill L.M, Alencar L.M, Sample P.A, Vasile C, Bowd.C. Long-term Intraocular Pressure Fluctuations and Risk of Conversion from Ocular Hypertension to Glaucoma. Ophthalmology. 2008;115:934-40.
40. Caprioli J, Coleman. Intraocular pressure fluctuation a risk factor for visual field progression at low intraocular pressure in the anvanced glaucoma intervention study. ophthalmology. 2008;115:1123-9.
41. Lee PP, Walt WJ, Rossenblatt LC, Siegartel LR, Stern LS. Association between intraocular pressure variation and glaucoma progression : data from a united states chart review. Am J Ophthalmol. 2007;144:901-7.
42. Nomura Y.Nakakura S. Effect of travoprost on 24-hour intraocular pressure in normal tension glaucoma. Clinical Opthalmology. 2010;4:643-7.
43. Dubiner HB., Noecker R,. Sustained intraocular pressure reduction throughout the day with travoprost ophthalmic solution 0.004%. Clinical Ophthalmology 2012;6:525-31.

44. Sit AJ, Weinreb NR, Jonathan G. Crowston GJ, Daniel F. Kripke DF, Liu JHK. Sustained effect of travoprost on diurnal and nocturnal intraocular pressure. Am J Ophthalmol. 2006;141:1131-3.
45. Larsson LI. Intraocular Pressure over 24 Hours after Repeated Administration of Latanoprost 0.005% or Timolol Gel-forming Solution 0.5% in Patients with Ocular Hypertension. ophthalmology. 2001;108:1439-44.
46. Konstas A.G.P, Mantziris DA, Cate EA, Stewart W.C. Effect timolol on the diurnal intraocular pressure in exfoliation and primary open angle glaucoma. Arch Ophthalmol. 1997;115:975-9.
47. Orzalesi N, Rossetti L, Invernizzi T, Bottoli A, Autelitano A. Effect of timolol, latanoprost, and dorzolamide on circadian IOP in glaucoma or ocular hypertension. Invest Ophthalmol Vis Sc. 2000;41:2566-73.
48. Konstas AGP, Quaranta L, Mikropoulos D.G,Nasr M.B, Russo A, Jaffee H.A,Stewart J, Stewart W.C. Peak intraocular pressure and glaucomatous progression in primary open-angle glaucoma. J Ocul Pharmacol Ther. 2012;28.
49. Wilensky JT, Gieser DK, Mori MT. Self tonometry to manage patients with glaucoma Am J Ophthalmol. 1987;105:1072-5.