Original Article

Comparison of Intraocular Pressure Lowering Effect of Travoprost and Timolol / Dorzolamide Combination in Primary Open Angle Glaucoma

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Purpose: To compare the efficacy of once daily travoprost 0.004% and twice daily Timolol 0.5% plus dorzolamide 2% combination in primary open angle glaucoma.

Material and Methods: This study was conducted at outpatient department, Ophthalmology unit, Khyber Teaching Hospital, Peshawar. Study design was randomized controlled trial and (group B receiving Timolol 0.5% and Dorzolamide 2% was considered as control group) the duration of the study was 6 months in which a total of 136 patients were included. All cases included in the study were diagnosed as cases of primary open angle glaucoma. Patients were divided into two groups i.e. A and B with each group having 68 patients. Patients in group A were given Travoprost 0.004% eye drops daily and patients in group B were given eye drops having combination of Timolol 0.5% and Dorzolomide 2% twice daily. Patients were advised to come at 6 weeks interval for follow up. At each follow up visit, IOP was recorded.

Results: Mean age in Group A was 53 ± 13.26 years while in Group B was 55 ± 14.31 years. In Group A 56% patients were male and 44% patients were female where as in Group B 59% patients were male and 41% patients were female. Our results show that Timolol + Dorzolamide was more effective than Travoprost as Timolol + Dorzolamide cause reduction in IOP of at least 20% in 84% patients while Travoprost cause reduction in IOP of at least 20% in 80% patients. Also p-value calculated at six week is statistically significant).

Conclusion: Our study concludes that dorzolamide with timolol is more efficacious than Travoprost in open angle glaucoma.

Key Words: Primary open angle glaucoma, travoprost, Timolol plus dorzolamide.

Glaucoma is one of the most common causes of permanent visual loss all around the world,[1] affecting about 60 million people worldwide[2]. In Pakistan, it is the fourth commonest cause of visual loss[3]. Glaucoma is characterized by optic nerve degeneration causing visual field defects and is usually associated with raised intraocular pressure (IOP)[4]. The main aim of treatment is to lower the intraocular pressure to preserve the vision and prevent progressive optic nerve degeneration[5]. Various treatment options include medical therapy, laser and surgical treatment. Timolol a beta-blocker acts by decreasing aqueous secretion. It has been found to be effective for treatment in all types of glaucoma[6]. Dorzolamide causes highly selective inhibition of carbonic anhydrase II isoenzyme present

on the ciliary processes in the eye which lowers the aqueous humor production and intraocular pressure[7]. Dorzolamide and Timolol are also used in combination with additive therapeutic effect. The efficacy of fixed combination of Timolol and Dorzolamide (FCDT) is well established. The clinical efficacy of (FCDT) defined as 20% or more reduction in mean intraocular pressure was found to be 82.9% in a study conducted by Andrew et al[8].

Travoprost, a prostaglandin analog is one of the newer anti-glaucoma drugs. It can strongly lower intraocular pressure[9]. The clinical efficacy of Travoprost, (defined as 20% or more reduction in mean IOP) was found to be 58.8% in a study conducted by Yuya Nomura et al[10]. Another study showed that 64.2% of the patients treated with Travoprost had marked reduction in intraocular pressure[11]. Trovoprost offers better patient compliance as it is given in once daily dose as opposed to twice daily dose for FCDT and hence Trovoprost is emerging as an alternative to the FCDT[12] due to cost effectiveness and better compliance.

Studies comparing the clinical efficacy of Trovoprost against the traditional FCDT combination are scarce. Moreover the clinical efficacy of Trovoprost is yet to be evaluated in our local population. Our study aims to assess the clinical efficacy of the newer drug Travoprost 0.004% against the established combination of Timolol and Dorzolamide in our local population. On the basis of this study, if Travoprost is found to be effective, this can be prescribed in routine instead of Timolol plus dorzolamide for patients with primary open angle glaucoma, with better compliance and safety profile.

MATERIAL AND METHODS

Patients with open angle glaucoma were selected from outpatient department, Department of Ophthalmology, Khyber Teaching Hospital, Peshawar as per operational definition. The purpose and benefits of the study were explained to the patient and the patient was explained that this research study is being done purely for research and a written informed consent was obtained, if agreed upon.

Patient compliance was stressed upon by education of the patient, relatives and by checking of the used bottles by patient.

Patients with newly diagnosed primary open angle glaucoma with either gender between the ages of 15 to 60 years were included in the study. Exclusion criteria were: Patients with IOP > 30, advanced visual field loss, CDR > 0.8 or best corrected visual acuity < 6/60 (these patients have advanced disease and require more aggressive treatment and this may act as confounder and affect the results of the study), patients in whom beta blockers are contraindicated e.g. patients with COPD, asthma, sinus bradycardia, heart block, and patients using drugs which can affect the intraocular pressure e.g. patients already on anti-glaucoma medications or on systemic beta blockers.

After inclusion in the study, patients was divided into group A and group B by lottery method i,e first patient went either into Group A or Group B by simple lottery and the subsequent patients were consectively placed in the respective groups.

Group A received once daily travoprost 0.004% and B received twice daily timolol 0.5% plus dorzolamide 2% combination. In both groups, detailed history was taken followed by complete examination including assessment of best corrected visual acuity (BCVA) using Snellen chart; pupillary reaction, anterior segment examination with slit-lamp; baseline IOP measurement with Goldman applanation tonometer; anterior chamber angle assessment with Goldman goniolens; fundus examination with direct ophthalmoscope and 90 D lens and perimetry (Humphrey's). The patient was advised to come at 6 weeks interval for follow up. At each follow up visit, IOP was recorded. Efficacy was defined as at least 20% reduction in the intraocular pressure from the baseline, at 6 weeks follow up, measured on tonometry.

All the relevant data was recorded in a pre-designed printed proforma. Those patients who developed drug side effects and those who don't come for follow up were omitted from the study. Confounders and bias in the study was controlled by strictly following the inclusion and exclusion criteria.

SPSS 10 was used for analysis of data. Efficacy in terms of reduction of IOP was compared between travoprost and FCDT. Mean ± standard deviation was calculated for quantitative variables; percentage and proportion were calculated for qualitative variables. Chi-square test was used to compare the efficacy in both groups. All the results were presented as tables and charts in a meaningful way. (P-Value had generated using student t-test for comparison of mean and chi-square test for comparison of percentages. P-Value < 0.05 had considered significant.)

RESULTS

A total of 136 (68 in each group) patients were included in the study. In Group A Mean age was 53 years with standard deviation ± 13.26 whereas in Group B mean age was 55 years with standard deviation ± 14.31.

Gender distribution among two groups was analyzed as in Group A 38 (56%) patients were male and 30 (44%) patients were female where as in Group B 40 (59%) patients were male and 28 (41%) patients were female (Table 1).

Table 1: Gender distribution (n = 136)

	Group "A" n (%)	Group "B" n (%)
Male	38 (56)	40 (59)
Female	30 (44)	28 (41)
Total	68	68

Group A: Travoprost
Group B: Timolol + dorzolamide.

Table 2: IOP at baseline (n = 136)

	Group "A" n (%)	Group "B" n (%)
24	7 (11)	6 (10)
25	11 (16)	12 (17)
26	11 (16)	10 (15)
27	13 (19)	14 (20)
28	15 (22)	14 (20)
29	8 (12)	8 (12)
30	3 (4)	4 (6)
Total	68	68

Group A: Travoprost
Group B: Timolol + dorzolamide.
P-value using t-test between two groups is 0.2511

Baseline IOP (mm Hg) among two groups was analyzed (Table 2). In Group A mean IOP was 27.05 mm Hg with SD ± 1.8401. Where as in Group B mean IOP was 26.67 mmHg with SD ± 2.0008 (Table 2).

Status of IOP after 6 weeks among two groups was analyzed (Table 3). In Group A mean IOP was 18.37 mmHg with SD ±1.9344. Where as in Group B mean IOP was 17.18 mmHg with SD ±1.8979 (Table 3). Comparison of mean baseline IOP and mean IOP at 6 weeks is shown in (Table 4).

Table 3: IOP at 6 weeks (n = 136)

	Group "A" n (%)	Group "B" n (%)
16	2 (3)	3 (4)
17	15 (22)	14 (21)
18	10 (14)	11 (16)
19	18 (27)	17 (25)
20	10 (14)	12 (18)
21	8 (12)	9 (13)
22	5 (8)	2 (3)
Total	68	68

Group A: Travoprost
Group B: Timolol + dorzolamide.
P-value using t-test between two groups is 0.0004

Table 4: Mean IOP (n = 136)

	Group "A"	Group "B"
Baseline	27.05 mm Hg ±1.8401	26.67 mm Hg ±2.0008
Mean		
Std. Deviation		
At 6 weeks	18.37 mm Hg ±1.9344	17.18 mm Hg ±1.8979
Mean		
Std. Deviation		

Group A: Travoprost
Group B: Timolol + dorzolamide.

Efficacy of the two drugs was analyzed as travoprost (Group A) was effective in 55 (80%) patients and was not effective in 13 (20%) patients. Whereas Timolol+ Dorzolamide (Group B) was effective in 57 (84%) patients and was not effective in 11 (16%) patients (Table 5) (comparison of mean IOP is shown in (Table 4).

Table 5: Efficacy (n = 136)

	Group "A" n (%)	Group "B" n (%)
Effective	55 (80)	57 (84)
Not Effective	13 (20)	11 (16)
Total	68	68

Group A: Travoprost
Group B: Timolol + dorzolamide.

DISCUSSION

Open angle glaucoma can cause permanent loss of vision. It remains asymptomatic and progress slowly until it is very severe and irreversible damage has occurred in one or both eyes. It is the second most common cause of irreversible blindness throughout the world[2].

A number of risk factors are responsible for progression of glaucoma but intraocular pressure IOP is currently the most important modifiable risk factor that can be used to prevent progression of glaucoma. According to Early - Manifest Glaucoma Treatment Study IOP reduction by at least 25% reduced progression damage in the treated group from 62% to 45% compared to an untreated group[13].

Mean intraocular pressure should be decreased to a patient dependent target pressure in order to prevent progressive glaucomatous damage and to preserve vision[8]. This target pressure depends on a number of factors, including baseline IOP, age of patient, status of optic disc and nerve fiber layer and functional damage assessed on visual field assessment[11].

The main objective of management of glaucoma is to preserve the visual functions and hence improve the individual's quality of life. The main treatment modality particularly of open angle glaucoma is medical treatment. Number of drugs is available which lowers the IOP either by enhancing the aqueous outflow or decreasing aqueous secretion. The main objective of medical treatment is to maintain IOP at lower level according to patient's target pressure with the minimum possible concentration, fewer numbers of drugs as well as using the safest drugs with limited local and systemic side effects[11].

Most commonly used drugs to decrease intraocular pressure in glaucoma are topical beta blockers. They are useful in all types of glaucoma and act by decreasing aqueous secretion. This IOP lowering effect however, decreases with time in approximately 10% of cases. This IOP lowering effect may be lost within a few days (short time escape) or may take months (long term drift)[5]. Beta blockers can cause local as well as systemic side effects including respiratory, cardiovascular, and metabolic side effects[5].

Our study results are similar to the results of some international studies, in one of two small (n 50 and 56), single – blind, parallel-group, single - center studies, Parmaksiz et al[13] had showed that the IOP-lowering effect of dorzolamide 2%/timolol 0.5% used twice daily was greater than that of travoprost 0.004% used once daily. The reduction in mean diurnal IOP (average of measurements noted at 08:00, 10:00 and 16:00 hours) from baseline with dorzolamide 2%/timolol 0.5% was superior to that with travoprost 0.004% (11.5 vs. 9.3 mm Hg; *P*0.05) after 6 months of treatment. In another single dose blind, parallel-group, single-center comparison Dorzolamide 2%/timolol 0.5% was less effective than travoprost 0.004%. In the parallel-group comparison, the reductions in mean diurnal IOP (average of measurements made at 08:00, 12:00, 16:00 and 20:00 hours) from baseline were significantly less with dorzolamide 2%/timolol 0.5% than with travoprost 0.004% after both 3 weeks of treatment (23.1% vs. 32.7%; *P* 0.01) and 6 weeks of treatment (21.7% vs. 30.7%; *P* 0.01). In a cross-over comparison, Franklin et al[14] had shown that the decrease in mean diurnal IOP (average of measurements made at 8:00 am, 10:00 am and 4:00 pm) from baseline following 3 months of treatment with dorzolamide 2%/timolol 0.5% (14.3%; *P* 0.0001 vs. baseline) was significantly less than that with travoprost 0.004% (18.4%; *P* 0.0001 vs baseline) and dorzolamide 2%/timolol 0.5%) and latanoprost 0.005% (22.1%; *P* 0.0001 vs. baseline) and dorzolamide 2%/timolol 0.5%).

The tolerability of a drug is the main barrier to compliance as shown by Strohmaier K et al[15]. Local burning, stinging, discomfort, and taste perversion are the most common adverse effects associated with dorzolamide[16]. Kalzuny et al[17] showed in their study that dorzolamide 2%/ timolol 0.5% fixed combination twice daily was generally well tolerated in large in large group of patients (n 177 – 492) given either as monotherapy or concomitantly, trials of 3 to 6 months duration which evaluated this fixed combination in relation to the individual components, or against other ocular hypotensive agents. In these studies 33% and

77% of patients receiving dorzolamide 2%/timolol 0.5% reported adverse effects. 10% to 68% reported drug-related adverse events. Most commonly reported ocular adverse event in majority of the trials was transient mild to moderate burning and/or stinging of the eye (5% – 41%). While the most common systemic adverse effect was dysgeusia (2% – 38%)[18].

Teus et al[19] in their study compared timolol 0.5% and brinzolamide 1%. The most common side effects with brinzolamide 1% were blurred vision and taste perversion; while ocular discomfort was less common.

Manni et al[20] in their study showed that of the 106 subjects, 79.2% preferred brinzolamide 1%/timolol 0.5% (*P* 0.0001). Ocular discomfort was significantly higher with dorzolamide 2%/timolol 0.5% than brinzolamide 1%/timolol 0.5% (2.9 vs 1.4, respectively; *P*0.0001). With dorzolamide 2%/timolol 0.5% instillation most common side effect was ocular pain and discomfort while with brinzolamide 1%/timolol 0.5% instillation it was transient blurred vision. Manni et al[20] observed in his study that brinzolamide 1%/timolol 0.5% showed significantly less ocular irritation (2.7% vs. 10.6%; *P* 0.0009) than dorzolamide 2%/timolol 0.5%.A statistically significant difference in conjunctival hyperemia in travoprost 0.004%/ timolol 0.5% group compared to dorzolamide 2%/ timolol 0.5% was shown by Teus et al in his study[19].

In a non-blind extension of one study, fixed combination was generally well tolerated for up to 1 year[21].

In 3 small, single-center studies, the IOP-lowering effects of dorzolamide–timolol fixed combination therapy were shown to be both better and worse than the efficacy of travoprost 0.004% monotherapy[22-24].

Fixed combination therapy with dorzolamide–timolol dosed twice daily was less efficacious than monotherapy with travoprost 0.004% dosed once daily in patients with OAG or OH as shown by Suzuki et al[22]. IOP reduction and percentage of IOP reduction were compared. Mean average IOP reductions from baseline at 3 and 6 weeks, were −7.5 mm Hg and −7.1 mm Hg respectively, for the travoprost monotherapy group and −4.8 mmHg and −4.5 mm Hg at 3 and 6 weeks, respectively, for the dorzolamide–timolol fixed combination therapy group. The better mean diurnal IOP reduction in the patients receiving travoprost 0.004% monotherapy compared with those receiving dorzolamide–timolol fixed combination therapy was statistically significant at both follow-up time points ($P < 0.01$).

CONCLUSION

Our study concludes that dorzolamide 2% with timolol 0.5% combination used twice daily is more efficacious than Travoprost 0.004% used once daily in primary open angle glaucoma.

Our results show that Timolol + Dorzolamide cause reduction in IOP of at least 20% in 84% patients while Travoprost cause reduction in IOP of at least 20% in 80% patients. Also p-value calculated at six week is statistically significant.

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REFERENCES

1. **Kumarasamy NA, Lam FS, Wang AL, Theoharides TC.** Glaucoma: Current and developing concepts for inflammation, pathogenesis and treatment. Eur J Inflamm. 2006; 4: 129-37.
2. **Quiiqley HA, Broman AT.** The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol. 2006; 90: 262-7.
3. **Dineen B, Bourne RR, Jadoon Z.** Causes of blindness and visual impairment in Pakistan. Br J Ophthalmol. 2007; 91: 1005-10.
4. **Hazin R, Hendrick AM, Kahook MY.** Primary open-angle glaucoma: Diagnostic approach and management. J Nati Med Assoc. 2009; 101: 46-50.
5. **Kanski JJ.** Glaucoma. In: Kanski JJ Clinical Ophthalmology. A systemic approach 6th ed. Butterworth Heinemann Elsevier 2007; 371-440.
6. **Izzotti A, Bagnis A, Saccà SC.** The role of oxidative stress in glaucoma. Mutat Res. 2006; 612: 105-14.
7. **Theelen T, Meulendij CF, Geurts DE.** Impact factors on intraocular pressure measurement in healthy subjects. Br J Ophthalmol. 2004; 88: 1510-1.
8. **Lodhi AA, Talpur KI, Khanzada MA.** Latanoprost 0.005% v/s timolol maleate 0.5% pressure lowering effect in primary open angle glaucoma. Pak J Ophthalmol. 2008; 24 (2): 68-72.
9. **Macleod SM, Clark R, Forrest J, Bain M, Bateman N, Azuara-Blanco A.** A review of glaucoma treatment in Scotland 1994-2004. Eye 2004; 22: 251-5.
10. The European Glaucoma Prevention Study (EGPS) Group. Results of the European Glaucoma Prevention Study. Ophthalmology. 2005; 112: 366-75.
11. **Parikh RS, Parikh SR, Navin S, Arun E, Thomas R.** Practical approach to medical management of glaucoma. Indian J Ophthalmol. 2008; 56: 223-30.
12. **Sharma R, Kohli K, Kapoor B, Mengi RK, Sadotra P, Verma U.** Comparative effect of timolol, levobunolol and betaxolol on IOP in patients of chronic simple glaucoma. JK science. 2005; 7: 61-4.
13. **Parmaksiz S, Yuksel N, Karabas VL.** A comparison of travoprost, latanoprost, and the fixed combination of dorzolamide and timolol in patients with pseudoexfoliation glaucoma. Eur J Ophthalmol. 2006; 16: 73–80.
14. **Franklin LM, da Silva LJ.** Comparison of the efficacy and safety of travoprost with a fixed – combination of dorzolamide and timolol in patients with open – angle glaucoma or ocular hypertension. Curr Med Res Opin. 2006; 22: 1799–805.
15. **Strohmaier K, Snyder E, DuBiner H.** The efficacy and safety of the dorzolamide-timolol combination versus the concomitant administration of its components. Dorzolamide-Timolol Study Group. Ophthalmology. 1998; 105: 1936–44.
16. **Sevda AK, Semih A, Ahmet A, Nurver O, Tomris S, Osman O.** The Effects of Topical Antiglaucoma Drugs as Monotherapy on the Ocular Surface: A Prospective Study. J. Ophthal. 2014: 112-120.
17. **Kalzuny J, Szaflik J, Czechowicz-Janicka K.** Timolol 0.5%/ dorzolamide 2% fixed combination versus timolol 0.5%/pilocarpine 2% fixed combination in primary open angle glaucoma or ocular hypertensive patients. Acta Ophthalmol Scand. 2003; 81: 349–54.
18. **Cvenkel B, Stewart JA, Nelson LA, Stewart WC.** Dorzolamide/timolol fixed combination versus latanoprost/timolol fixed combination in patients with primary open-angle glaucoma or ocular hypertension. Curr Eye Res. 2008; 33: 163–8.
19. **Teus MA, Miglior S, Laganovska G.** Efficacy and safety of travoprost/timololvsdorzolamide/timolol in patients with open-angle glaucoma or ocular hypertension. Clin Ophthalmol. 2009; 3: 629–36.
20. **Manni G, Denis P, Chew P.** 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. 2009; 18: 293–300.
21. **Mundorf TK, Rauchman SH, Williams RD, Notivol R.** Brinzolamide/ Timolol Preference Study Group. A patient preference comparison of Azarga (brinzolamide/timolol fixed combination) vsCosopt (dorzolamide/timolol fixed combination) in patients with open-angle glaucoma or ocular hypertension. Clin Ophthalmol. 2008; 2: 623–8.
22. **Suzuki ER.** Comparison of the efficacy and safety of travoprost with a fixed-combination of dorzolamide and timolol in patients with open-angle glaucoma or ocular hypertension. Curr Med Res Opin. 2006; 22: 1799-805.
23. **Nicholas PB, José LR, Robert MF.** Safety, tolerability, and efficacy of fixed combination therapy with dorzolamide hydrochloride 2% and timolol maleate 0.5% in glaucoma and ocular hypertension. Clin Ophthalmol. 2010; 4: 1331–46.
24. **Jin-WC, Shi-WC, Lian-DG, Guo-CL, Rui-LW.** Pressure-Lowering Effects of Commonly Used Fixed-Combination Drugs with Timolol: A Systematic Review and Meta-Analysis. PLoS One. 2012; 7: e45079.