

## A Comparative Study of Efficacy and Safety of Non-fixed Combination of Dorzolamide/timolol and Latanoprost/Timolol in Open Angle Glaucoma or Ocular Hypertension

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**Abstract:** The Aim of this study was to compare the clinical efficacy and safety of non-fixed combination (NFC) of dorzolamide (2.0%)/timolol maleate (0.5%) versus NFC of latanoprost (0.005%)/timolol maleate (0.5%) regarding reduction of intra ocular pressure in patients with primary open angle glaucoma. This was a 12-week, randomized, open label, parallel group study with primary open angle glaucoma (IOP range: 24 – 36 mmhg), which included 40 subjects in dorzolamide/timolol group [dorzolamide (2.0%) instilled twice daily and timolol maleate (0.5%) twice daily] and 40 subjects in latanoprost/timolol group [latanoprost (0.005%) instilled once daily, timolol maleate (0.5%) twice daily]. IOP was measured at baseline, 4 and 12 weeks at 10 am. Adverse events were recorded at each visit. The difference in reduction of IOP in two treatment groups from baseline to 12 weeks was the main outcome measure. Mean IOP was similar at baseline for both groups. Absolute reduction in IOP from baseline to 12 weeks was 9.6 mmhg in dorzolamide/timolol group ( $P < 0.001$ ) and 9.7 mmhg in latanoprost/timolol group ( $P < 0.001$ ). No significant difference was found regarding reduction of IOP between the groups ( $P < 0.85$ ). Both treatments were well tolerated. NFC of dorzolamide/timolol and latanoprost/timolol showed comparable efficacy in reducing IOP. They were also comparable regarding safety profile.

**Keywords:** Glaucoma, Non-fixed combination therapy, dorzolamide/timolol, latanoprost/timolol.

## INTRODUCTION

Glaucoma is a progressive optic neuropathies in which progressive degeneration of retinal ganglion cells and their axons occur, which results a distinct appearance of optic disc and causes gradual impairment of vision. Various risk factors may contribute to the development of glaucoma; intraocular pressure is the only proven treatable risk factor [1]. The most common type of glaucoma is primary open angle glaucoma (POAG) which accounts for three quarters (74%) of all glaucoma cases [2]. In 2013 number of POAG cases were 44 million globally, which is expected to increase to 53 million by 2020 due to population ageing [3]. In India, estimated number of glaucoma among persons aged 40 years and above is approximately 11.2 million. Among them, POAG is estimated to affect about 6.48 million [4]. Medical management of glaucoma often requires combination of drugs which lower intraocular

pressure (IOP) that usually act synergistically. The beta receptor antagonist timolol, acts by decreasing the production of aqueous humour by the ciliary epithelium has often been combined with latanoprost, a prostaglandin analogue that acts by increasing aqueous outflow, a mechanism complementary to that of timolol [5, 6]. Dorzolamide, a carbonic anhydrase inhibitor, also suppresses the production of aqueous humour, used in treatment of glaucoma, often in combination with other drugs [7, 8].

Fixed dose combination (FC) of these different groups of drugs is an important part of glaucoma management [9, 10]. In some Government set ups drugs are procured in large scales from different suppliers and supplied free of cost to the patients, in such cases it may not be possible to supply all the drugs as per required formulations of drugs like FC. This study was

conducted in a Regional Institute of Ophthalmology (RIO) in Eastern India which is a Government institute. In this institute all the medicines are supplied by the state Government and distributed free of cost to the patients through the pharmacies of the institute. NFC eye drops are supplied as per policy of state government. The purpose of this study was to compare the clinical efficacy and safety of NFC dorzolamide (2.0%)/timolol maleate (0.5%) versus NFC latanoprost (0.005%)/timolol maleate (0.5%) regarding reduction of intra ocular pressure in patients with POAG.

**MATERIALS AND METHODS**

This was a 12-week, randomized, open label, parallel group study conducted at outpatient department (OPD) of Regional Institute of Ophthalmology (RIO) in association with Department of Pharmacology, Medical College, Kolkata, West Bengal. Newly diagnosed subjects of unilateral or bilateral POAG (IOP range: 24-36 mmhg), diagnosed by applanation tonometry and gonioscopy of either sex and age 40 years and above were included in the study. Subjects with angle closure glaucoma, secondary open angle glaucoma, other ocular diseases and known allergy to the study drugs were excluded. Following a pilot study with 10 patients, the required sample size turned out to be 40 per group considering Type 1 error 5% and power of study 80% to detect the effect size 3 mm Hg with standard deviation of 2.5. After randomization using block randomization method, subjects were included in either dorzolamide/timolol group or latanoprost/timolol group. Subjects in dorzolamide/timolol group were asked to administer dorzolamide (2.0%) and timolol maleate (0.5%) eye drop, one drop each, one after another in the

affected eye/eyes twice daily in the morning and evening. Those in latanoprost/timolol group were asked to administer one drop of latanoprost (0.005%) eye drop in the evening and one drop of timolol maleate (0.5%) eye drop twice daily in the morning and evening. Study drugs were supplied free of cost from the pharmacy of the hospital. IOP was measured at baseline, fourth and twelfth week at 10 AM. On the first visit a complete medical, ocular and treatment history were taken and systemic and eye examinations including visual acuity testing, slit lamp examination and ophthalmoscopy were done. Any concomitant medications for other illness were asked to continue. Institutional ethics committee approval was obtained. Informed consent was taken from the subjects. Data regarding adverse effects were collected for safety analysis.

Summary statistics of numeric variables were expressed as mean and standard deviation and categorical data as proportions. Numeric parametric data were analyzed using paired *t*-test, unpaired *t*-test, and repeated measures analysis of variance (ANOVA) according to the condition; categorical data were analyzed by Fisher's exact test. The 95% confidence interval (CI) of the difference between means was determined and P <0.05 was considered statistically significant.

**RESULTS**

A total of 80 subjects were included in the study. 40 were randomized in each group. Both the groups were similar at baseline regarding age, sex and mean IOP (Table1).

**Table-1: Baseline demographic variables in group A and group B**

Variable	Dorzolamide/timolol group (n=40)	Latanoprost/timolol group (n=40)	P value
Age (years)	40.22(8.8)	40.27(8.6)	0.9796
Gender	Male	21	1.00
	Female	19	
Mean IOP (mmhg)	29.35( 2.9)	29.4 (2.8)	0.92

All variables except gender were expressed as mean ± SD.

Significant reduction of IOP was observed in both groups (dorzolamide/timolol: P < 0.001,

latanoprost/timolol: P < 0.001) at 4 weeks and 12 weeks (Table 2).

**Table-2: Comparison of mean IOP (mmHg) within groups**

	Baseline	4 week	12 week	P value
Group A	29.35 (2.9)	25.05 (2.3)	19.65 (1.8)	<0.0001
Group B	29.4 (2.8)	24.92 (2.7)	19.74 (1.8)	<0.0001

Absolute reduction in IOP from baseline to 4 weeks was 4.3 mmhg in dorzolamide/timolol group and 4.4 mmhg in latanoprost/timolol group. No significant difference was found between the groups (P < 0.55) at 4 weeks (Table 3). At 12 weeks, absolute reduction in

IOP from baseline was 9.7 mmhg in dorzolamide/timolol group (P < 0.001) and 9.6 mmhg in latanoprost/timolol group (P < 0.001). No significant difference was found between the groups (P < 0.85) at 12 weeks also (Table 3).

**Table-3: Comparison of absolute reduction of mean IOP (mm Hg)**

	Group A	Group B	P value
4 week	4.3 (1.5)	4.4 (1.4)	0.55
12 week	9.7 (2.1)	9.6 (1.8)	0.85

In general both the groups tolerated the drugs well. However in dorzolamide/timolol group adverse effects noticed were conjunctival hyperemia, stinging sensation, foreign body sensation, photophobia and eye

pain. On the other hand, conjunctival hyperemia, stinging sensation, foreign body sensation were main adverse effects in latanoprost/timolol group (Table 4).

**Table-4: Adverse effects of study drugs**

Ocular adverse effects	Dorzolamide/timolol group (n=40)	Latanoprost/timolol group (n=40)
Conjunctival hyperemia	2	6
Burning/stinging sensation	3	2
Foreign body sensation	2	2
Photophobia	2	0
Eye pain	6	0

None of the adverse effects was severe enough to discontinue the medication in any group. All were mild and self-limiting requiring only supportive care.

#### DISCUSSION

This 12 week, randomized, parallel group study is the first study undertaken in the eastern part of India in a Regional Institute of Ophthalmology in West Bengal. In previous studies, drugs were administered in fixed dose formulations, but in this study drugs were administered in NFCs. There was significant reduction of IOP in dorzolamide/timolol ( $P < 0.001$ ) and latanoprost/timolol groups ( $P < 0.001$ ) from baseline to study end, *i.e* after 12 weeks. However no significant reduction of IOP was observed between the groups at 4 weeks ( $P < 0.55$ ) and 12 weeks ( $P < 0.85$ ).

The finding of equivalent effectiveness parallels the result of previous other studies. In one crossover study of 32 newly diagnosed, open-angle glaucoma, treatment-naive patients, found that both treatments significantly reduced the IOP levels (measured once in the morning) between baseline and month 1 [11]. In another randomised controlled trial reductions in IOP from baseline to 12 weeks was by -9.7 mmhg for latanoprost/timolol and -9.5 mmhg for dorzolamide/timolol, indicated that neither was inferior to other [12], whereas a 12 week randomized, parallel group study in 253 subjects found that mean IOP level after 3 months of treatment were significantly lower in the latanoprost/timolol group ( $P < 0.01$ ) than the dorzolamide/timolol ( $P < 0.05$ ) [13]. In one 12 week randomized open label, parallel group study from India, latanoprost/timolol and dorzolamide/timolol was compared and it was found that latanoprost/timolol showed statistically significant effectiveness at 12 weeks [14]. In another study done in 2008 found that patients treated with dorzolamide/timolol fixed combination (FC) and latanoprost/timolol FC have statistically similar ocular hypotensive effect [15].

In our study, regarding safety parameters, it was found that none of the adverse effects were severe enough to withdraw the subjects from the study. Conjunctival hyperemia was found to be the most common in latanoprost/timolol group and eye pain was the most common in dorzolamide/timolol group. This is consistent with previous studies [12, 14].

#### CONCLUSION

The present study reveals that there is no significant difference regarding reduction of IOP in open angle glaucoma patients by NFC of dorzolamide (2.0%)/timolol maleate (0.5%) versus NFC of latanoprost (0.005%)/timolol maleate (0.5%). Their safety profile is also comparable.

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