

# The intraocular pressure lowering efficacy of 0.5% timolol maleate versus 1% brinzolamide in cases of primary open angle glaucoma and ocular hypertension

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## ABSTRACT


**Objectives:** The aim of this study was to compare the intraocular pressure lowering efficacy of timolol maleate with brinzolamide in cases of primary open angle glaucoma and ocular hypertension.

**Methods and Materials:** This prospective, open, randomized, parallel group, comparative study was conducted in patients coming to the Department Of Ophthalmology, Rajindra Hospital attached to Government Medical College, Patiala. 60 patients of POAG or ocular hypertension were selected. Patients were then randomized into two groups (group I, II) and received 0.5 % timolol maleate and 1% brinzolamide respectively. Effectiveness of the drugs was calculated in terms of mm Hg fall in mean intraocular pressure at the end of 3 months. The observations thus made in both groups were compared.

**Results:** In group I the mean pre-treatment IOP, mean post-treatment IOP and mean reduction in IOP were  $24.30 \pm 0.99$ ,  $18.53 \pm 1.22$  and  $5.77$  (23.74%) for peak measurements, and  $24.50 \pm 1.08$ ,  $18.80 \pm 1.22$  and  $5.70$  (23.27%) for trough measurements. In group II the mean pre-treatment IOP, mean post-treatment IOP and mean reduction in IOP were  $24.33 \pm 0.96$ ,  $19.43 \pm 1.14$  and  $4.90$  (20.14%) for peak measurements, and  $24.57 \pm 0.97$ ,  $19.73 \pm 1.11$  and  $4.84$  (19.69%) for trough measurements.

**Conclusions:** In conclusion, there was a statistically significant difference between the IOP lowering in the two groups with timolol maleate producing more reduction in IOP than brinzolamide.

**Key-words:** Brinzolamide; Glaucoma; IOP; Ocular hypertension; POAG; Timolol.

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## INTRODUCTION

More than 67 million persons worldwide are affected by glaucoma, of which about 10% or 6.6 million are estimated to be blind.<sup>[1]</sup> According to National Survey on Blindness 2001- 2002, prevalence of blindness in India is 1.1 %. The foremost cause of blindness in India being cataract, accounts for 62.6%, whereas glaucoma accounts for 5.8%.<sup>[2]</sup>

Glaucomatous optic neuropathy is the common denominator to all forms of glaucoma and is derived from multiple risk factors of which raised IOP is the most important.<sup>[3]</sup> Primary open angle glaucoma is defined by 3 criteria which are an IOP consistently above 21 mmHg in at least on eye, an open, normal appearing anterior chamber angle with no apparent ocular or systemic abnormality that might account for elevated IOP, and typical glaucomatous visual field and/or optic nerve head damage. Ocular hypertension is defined as an intraocular pressure consistently above 21 mmHg in the absence of the other two criteria.<sup>[4]</sup>

Since IOP is the only risk factor amenable to therapy, lowering of IOP is the treatment of choice to impede further neuronal damage.<sup>[5]</sup> Any medical or surgical treatment that controls the IOP will be an effective therapy for glaucoma. Medical treatment is the first therapeutic approach while surgery is reserved for cases that cannot be controlled by drugs.<sup>[6]</sup> Currently, there are five major classes of drugs used for the treatment of glaucoma which are cholinergic agonists, alpha adrenergic- receptor agonist, beta adrenergic- receptor antagonists, topical and systemic carbonic anhydrase inhibitors and hypotensive lipids i.e. prostaglandin analogues and prostamides.<sup>[7]</sup>

Timolol maleate is a non-selective  $1\beta$  and  $2\beta$  adrenergic antagonist that does not have substantial membrane-stabilizing properties and intrinsic sympathomimetic activity.  $\beta$  -adrenergic antagonists reduce IOP by decreasing aqueous humor formation without changing the outflow pathway. Timolol enters the eye rapidly; following topical administration, IOP begins to fall in 30–60 minutes, becomes lowest in 2 hours, and then in 24–48 hours, returns to normal.<sup>[8]</sup>

Brinzolamide is a carbonic anhydrase inhibitor indicated in patients with ocular hypertension or open-angle glaucoma for the treatment of elevated intraocular pressure. Pharmacologically, it is a highly specific, reversible, non-competitive and potent inhibitor of carbonic anhydrase II (CA-II)<sup>[9]</sup>, because of which it is

able to suppress formation of aqueous humour and thus decrease IOP. Following topical administration, brinzolamide is absorbed into the systemic circulation where due to its affinity for CA-II, brinzolamide distributes extensively into the RBCs and exhibits a long half-life of approximately 111 days.

### MATERIALS AND METHODS

In this prospective, open, randomized, parallel group, comparative study, 60 patients of POAG or ocular hypertension attending the Outpatient Department of Ophthalmology, Govt. Medical College, Patiala were included. Due permission from the ethical committee of the institute was obtained. The patients fulfilling the inclusion criteria and having none of the exclusion criteria were enrolled in the study after obtaining written informed consent. Patients of a minimum age of 18 years, having unilateral/bilateral primary open angle glaucoma/ ocular hypertension with an IOP > 21 mm Hg and  $\leq$  30 mm Hg were included in the study. Exclusion criteria for patients were history of acute angle closure glaucoma, established diagnosis of secondary glaucoma, closed anterior chamber angle, ocular inflammation, ocular infection, pregnant and lactating females, patient unable to attend follow up, known sensitivity to drug, chronic use of ocular

medication other than the glaucoma medications and patients having any contraindication to the use of beta blockers and carbonic anhydrase inhibitors.

Patients who were already on any other anti-glaucoma treatment were taken up for study after a washout period of 7 days for miotics and carbonic anhydrase inhibitors, 14 days for alpha and beta adrenergic agonists and 21 days for beta blockers, prostaglandin analogues and combination drugs. Patients requiring treatment for bilateral POAG were treated for both eyes but the right eye was the study eye. Patients selected were randomised into two groups of 30 each. Group I and Group II instilled 1 drop of timolol 0.5% and brinzolamide 1% respectively, into study eye twice daily at 9.00 a.m. and 9.00 p.m. for 12 weeks. During the study patients visited the hospital on day 0, week 4, week 8 and week 12. IOP readings were taken from the study eye with the Goldmann applanation tonometer at each visit. IOP was measured on day 0 at 9.00 a.m. and 11.00 a.m before administration of the study drugs to get the baseline IOP and then on each follow-up visit at 9.00 a.m. and 11.00 a.m. to record the peak and trough of each medication. Observations thus made were recorded and subjected to statistical analysis at the end of the study.

**Table-1: Sex Distribution of Patients in Group I and Group II**

Gender	Group I		Group II		Total	
	Timolol Maleate 0.5%		Brinzolamide 1%			
	No. of Patients	%age	No. of Patients	%age	No. of Patients	%age
Female	14	46.67%	11	36.67%	25	41.67%
Male	16	53.33%	19	63.33%	35	58.33%
Total	30	100%	30	100%	60	100%

**Table-2: Mean IOP in Group I and Group II at Different Points of Time**

Visit	GROUP I (TIMOLOL MALEATE 0.5%)		GROUP II (BRINZOLAMIDE 1%)	
	At 9:00 am Mean $\pm$ SD (mmHg)	At 11:00 am Mean $\pm$ SD (mmHg)	At 9:00 am Mean $\pm$ SD (mmHg)	At 11:00 am Mean $\pm$ SD (mmHg)
Day 0	24.50 $\pm$ 1.08	24.30 $\pm$ 0.99	24.57 $\pm$ 0.97	24.33 $\pm$ 0.96
Week 4	18.77 $\pm$ 1.17	18.33 $\pm$ 1.16	19.60 $\pm$ 0.93	19.30 $\pm$ 1.06
Week 8	18.73 $\pm$ 1.08	18.50 $\pm$ 1.19	19.63 $\pm$ 0.99	19.43 $\pm$ 0.97
Week 12	18.80 $\pm$ 1.22	18.53 $\pm$ 1.22	19.73 $\pm$ 1.11	19.43 $\pm$ 1.14

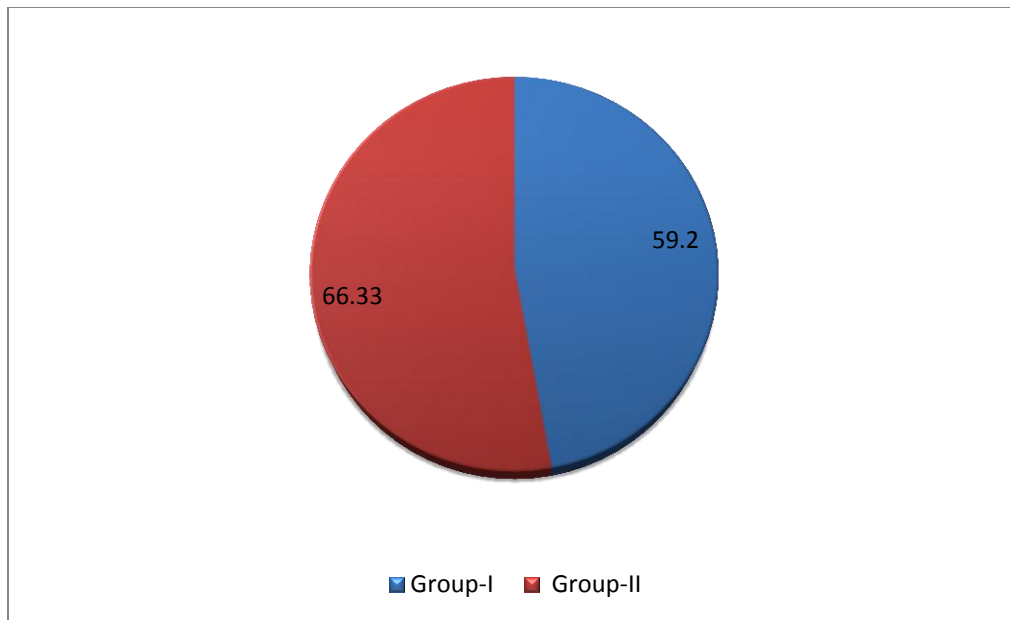


Fig. 1: Age Distribution in the Groups

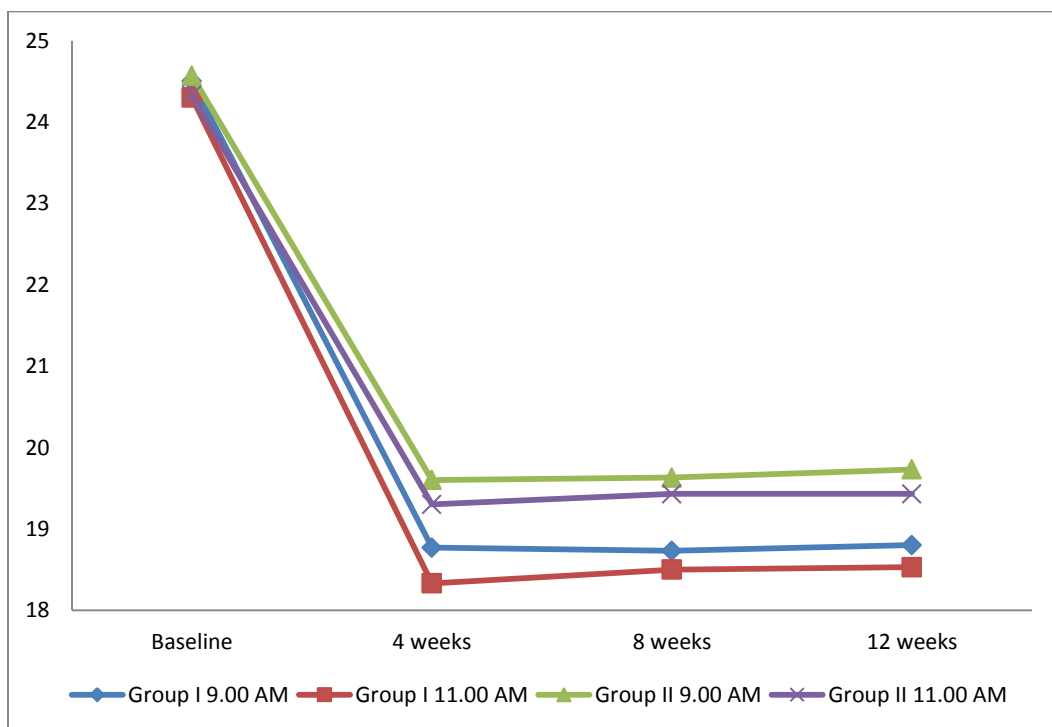


Fig. 2: Mean IOP in Group I and Group II at Different Points of Time

**RESULTS**

There were no statistically significant differences between the two groups regarding all the parameters of patient profile. In the 60 patients included in the study the mean age was 62.77 years. Mean age in group I was 59.2 years and in group II was 66.3 years. Overall in the study 58.33% of the patients were male and 41.67% were female.

In our study, timolol maleate 0.5% showed a consistent reduction in IOP when compared to baseline values at

all follow-up visits, including both peak and trough readings, taken at 4 weeks (5.97 mmHg and 5.73 mmHg), 8 weeks (5.80 mmHg and 5.77 mmHg) and 12 weeks (5.77 mmHg and 5.70 mmHg). All the values were extremely significant when compared with baseline readings. Maximum fall in IOP was observed at the first follow-up visit at 4 weeks followed by a slight rise in readings at the final visit. Thus, at the end of 12 weeks IOP reduction with timolol maleate was 23.74% for peak and 23.27% for trough readings.

IOP values compared with the baseline with brinzolamide 1% also demonstrated a constant lowering at the end of 4 weeks (5.03 mmHg and 4.97 mmHg), 8 weeks (4.90 mmHg and 4.94 mmHg) and 12 weeks (4.90 mmHg and 4.84 mmHg) with all readings being extremely significant compared to the baseline. Treatment with brinzolamide also produced maximum IOP lowering at 4 weeks followed by slight raise seen at 12 weeks. Final readings taken at 12 weeks showed IOP lowering of 20.14% for peak and 19.69% for trough readings.

Comparison between the two groups showed that across all time points and visits during the 12 week treatment period IOP lowering produced with timolol maleate 0.5% was more as compared to brinzolamide 1%. At the end of the study period, IOP lowering with timolol 0.5% was significantly more than brinzolamide 1% for both peak readings ( $p = 0.0045$ ) and for trough readings ( $p = 0.003$ ). Thus there was a statistically significant ( $p$  value  $< 0.05$ ) difference between the IOP reduction with timolol maleate 0.5% and brinzolamide 1%.

## DISCUSSION

Glaucoma is a potentially blinding disease, and constitutes one of the greatest problems in ophthalmologic care. Glaucoma is the leading cause of irreversible blindness worldwide and is second only to cataract as the most common cause of blindness overall.<sup>[1]</sup> Reduction of IOP to the normal range significantly reduces the risk of damage to the nerve fibres for the individual and consequent visual loss. It may even prevent further damage.<sup>[10]</sup> Medications lower IOP either by reducing the production or by increasing outflow of aqueous humour.

There are very few studies comparing brinzolamide with timolol maleate as monotherapy in cases of POAG and ocular hypertension especially in the Indian population. Our study aimed to compare the efficacy of these two drugs in such a population as monotherapy.

The efficacy of brinzolamide 0.3%–3% BD has been evaluated in several randomized double-blind, multicentre comparative clinical trials<sup>[11-19]</sup>. A dose-response study comparing brinzolamide in concentrations of 0.3%, 1%, 2%, and 3% demonstrated mean IOP reductions of 3 mmHg (11.3%), 4.3 mmHg (16.1%), 4.4 mmHg (16.1%), and 4.2 mmHg (15.4%), respectively. When diurnal IOP was measured, brinzolamide 1% or 3% reduced IOP significantly better than brinzolamide 0.3%<sup>[13]</sup>. At the end of our study, brinzolamide 1% showed reduction in IOP of 4.90 mmHg (20.14%) for peak and 4.84 mmHg (19.69%) for trough readings.

In their study Wang et al<sup>[19]</sup> (2004) concluded that a significant decrease in mean IOP was found after 6 weeks of treatment in both the brinzolamide group (-17.0%) and the timolol group (-19.7%), with no significant between-group difference in the control of IOP. When used twice a day, topical brinzolamide is as

effective as 0.5% timolol in lowering IOP in patients with open angle glaucoma. In our study, we also observed significant IOP lowering with both timolol 0.5% and brinzolamide 1% at each visit, but the IOP lowering with timolol 0.5% was significantly more than that produced with brinzolamide 1% across all time points.

Van der Valk et al<sup>[20]</sup> (2005) in their meta-analysis of randomized clinical trials of intraocular pressure-lowering effects of all commonly used glaucoma drugs, ranked IOP reduction with timolol 0.5% [peak, 27% (29% to 25%), and trough, 26% (28% to 25%)] more than that with brinzolamide 1% [peak, 17% (19% to 15%), and trough, 17% (19% to 15%)]. Thus the findings of their meta-analysis are in concordance with the results observed at the end of our present study.

In the present study, IOP reduction with timolol maleate 0.5% and brinzolamide 1% was 5.77 mmHg (23.74%) and 4.90 mmHg (20.14%), respectively at peak readings; and 5.70 mmHg (23.27%) and 4.94 mmHg (19.69%), respectively for trough readings. Comparison between the two groups showed that across all time points and visits during the 12 week treatment period IOP lowering produced with timolol maleate 0.5% was more as compared to brinzolamide 1%. There was a statistically significant ( $p$  value  $< 0.05$ ) difference between the IOP reduction with timolol maleate 0.5% and brinzolamide 1%. Thus in our study we concluded that treatment with timolol 0.5% was more effective than brinzolamide 1%.

In our study, the study period was only of 12 weeks, so data about long-term efficacy of the drugs could not be evaluated. A longer trial is needed to elicit any difference in the long term efficacy of the drugs.

The authors reveal no conflict of interest.

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