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# A comparison of the efficacy and safety of timolol in combination with dorzolamide, brimonidine or latanoprost in patients of primary open angle glaucoma

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**ABSTRACT**

The present study was undertaken to compare the efficacy and safety of timolol with dorzolamide, brimonidine or latanoprost in patients of primary open angle glaucoma. This prospective, observational study was conducted over one and a half year at the Regional Eye Institute, in patients of primary open angle glaucoma who were prescribed dorzolamide (2%) and timolol (0.5%) (DT), brimonidine (0.1%) and timolol (0.5%) (BT) or latanoprost (0.005%) and timolol (0.5%) (LT). Measurement of intraocular pressure (IOP) and indirect ophthalmoscopy was done at baseline and after 1, 3 and 6 months of treatment. Efficacy was assessed by the degree of reduction in intraocular pressure and change in cup-disc ratio. Adverse drug reactions (ADRs), if any, were recorded. The data was analysed using Student's 't' test and one-way ANOVA test. *P* value < 0.05 was considered to be statistically significant. Total number of 35 patients in DT group, 34 in BT group and 32 in LT group completed the study. At the end of 6 months, average reduction in IOP levels was 7.83, 9.39 and 9.73mmHg in DT, BT and LT groups respectively. Thus, a percent reduction of 29.4, 35.6 and 36.2 from baseline was observed in these groups respectively. While the reduction was maximum in LT group, there was no statistically significant difference between any of the groups at 1, 3 or 6 months. A total of 47 ADRs were reported, none of which required discontinuation. All three combinations are effective in reducing the IOP level in patients of primary open angle glaucoma and none appear to be superior to the others.

## INTRODUCTION

Primary open angle glaucoma (POAG) is an idiopathic disease of the retinal ganglion cells (RGCs) and optic nerve axons, having limited modalities of treatment. Globally it contributes significantly to the ocular morbidity and blindness. Glaucoma is known to be the second most common cause of blindness in world, next only to cataract, which in contrast is easy to manage and rarely threatens vision (Kingman, 2004; Resnikoff *et al.*, 2004). It is also estimated that in 2010, approximately 60.5 million people were affected by glaucoma with over 8.4 million becoming blind (Quigley and Broman 2006). Medical treatment of glaucoma is mostly focussed towards reduction of the intra-ocular pressure (IOP), an important risk factor. Surgery is an option only in those refractory to drugs. The drugs commonly used in the treatment are beta blockers, prostaglandin analogues, alpha receptor agonists, carbonic anhydrase inhibitors and cholinergic agonists. Timolol, a beta blocker, is considered the "gold standard" for treatment of glaucoma as per the US-FDA, against which all new medications must be compared prior to approval (Gupta *et al.*, 2008). Therefore timolol can be considered as an essential component of therapy. The Collaborative Initial Glaucoma Treatment Study (CIGTS) showed that after two years of treatment, more than 75% of patients needed two or more medications to reach their target IOP (Lichter *et al.*, 2001). Therefore when β-blockers alone are inadequate to control the IOP, other classes of agents may be needed as an add-on therapy. Timolol may be used in combination with latanoprost, trovaprost, dorzolamide, brinzolamide, brimonidine and infrequently with pilocarpine. These combinations show a varied efficacy in reducing the IOP, with latanoprost containing combinations faring better than others (Cheng *et al.*, 2012). However, a decision to choose a combination depends on the patient's response in achieving particular level of IOP (target pressure), tolerability to a particular drug and its cost

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as the treatment has to be taken lifelong. We, thus, felt that it was important to evaluate the commonly prescribed combinations. The present study aimed at comparing the efficacy and safety of timolol with dorzolamide, brimonidine or latanoprost in patients of POAG at a Regional Eye Institute affiliated with a tertiary care teaching hospital.

## MATERIALS AND METHODS

It was a prospective and observational study, conducted over a period of one and a half year from November, 2009 to April, 2011. After obtaining permission from the Institutional Ethics Committee, the investigator attended the glaucoma out-patient clinic twice a week. The patients, of either gender above 18 years of age, diagnosed with primary open angle glaucoma, not controlled with timolol alone and prescribed either dorzolamide (2%), brimonidine (0.1%) or latanoprost (0.005%) as a combination were included in the study. Those with a history of ocular inflammation or infection within last 3 months of baseline known to be sensitive to vehicle or drug, pregnant or lactating women and those who refused to participate were excluded from the study. The patients fulfilling the selection criteria were enrolled and written informed consent was taken. They were categorized into three groups according to the combinations prescribed by the ophthalmologist namely, dorzolamide, brimonidine or latanoporst with timolol. Detailed history of the patient was obtained and recorded in a pre tested Case Record Form along with findings from general examination, laboratory investigations, if any, and treatment given.

The intraocular pressure (IOP) was measured with a hand-held Perkin's applanation tonometer. An indirect ophthalmoscopy was done to measure the cup-disc ratio. A follow up evaluation of each patient was done at 1, 3 and 6 months after baseline visit. At each subsequent visit, IOP measurement and indirect ophthalmoscopy was repeated. Efficacy was assessed by the degree of reduction in intraocular pressure and change in cup disc ratio. Additionally, the patients were asked for adverse drug reactions (ADRs), if any, and the details were noted in an ADR reporting form. The data was entered in Microsoft Excel spreadsheet and analysed using Graph pad InStat (Trial), version 3.0.10.0. The intra-group analysis of IOP reduction was done using paired Student's t-test and inter-group analysis was done using one-way ANOVA test. *P* value < 0.05 was considered to be significant. The ADRs observed during the study were analysed for their causality using WHO-UMC scale (www.who-umc.org, 2009) and Naranjo's algorithm (Naranjo *et al.,* 1981), severity using Hartwig and Siegel scale (Hartwig *et al.,* 1992) and preventability using modified Schumock and Thornton criteria (Lau *et al.,* 2003).

## RESULTS

A total of 257 patients were enrolled, of which 101 (39.2%) completed the 6 month follow-up across all groups (35, 34 and 32 patients in DT, BT and LT group respectively). Around 60% (156/257) of the patients did not complete the study, the reasons being loss to follow-up (111), medication change (23) and surgical intervention (22). Majority of the patients belonged to the age group of 41-50 years in all three groups (range 26 to 77 years). Males were more commonly affected than females (total 57 males and 44 females out of 101 patients). The three groups were comparable with respect to the demographic parameters at baseline.

The most common presenting complaint among all the groups was dimness of vision (48). As POAG is common in elderly, 12 patients had a past history of cataract and all had been operated for the same. Acute iridocyclitis and chronic dacrocystitis were also noted in 2 patients in each group. There was a family history of glaucoma in 31 (30.6%) patients, out of which 5 patients had afflicted first degree relatives. Hypertension (45) and diabetes mellitus (29) were frequent co-morbidities observed among the patients. Angiotensin converting enzyme inhibitors were the most common concomitant medication taken followed by beta adrenergic blockers and angiotensin receptor blockers. Myopia was observed in 21 patients.

### Intra-ocular pressure (IOP)

The mean IOP at baseline for DT, BT and LT groups was 25.7±4.2, 26.3±5.9 and 26.5±4.8 mm Hg respectively with no significant difference (p>0.1) between the groups. After 1 month of treatment (1$^{st}$ follow up), the mean reduction of IOP from baseline was 2.65, 4.95 and 5.31 mm Hg in DT, BT and LT groups respectively, all considered statistically significant as compared to the baseline ($p$<0.05) (Table 1). Thus, approximately 10-20% reduction in IOP was observed at 1$^{st}$ follow up in all groups. The reduction was, however, maximum in case of LT group (19.7%). Five patients each in BT and LT groups achieved a reduction of more than 30% compared to baseline. After 3 months of treatment (2$^{nd}$ follow up), the mean reduction of IOP from baseline was 5.52, 7.51 and 7.76 mm Hg in DT, BT and LT groups respectively, all considered statistically significant as compared to the baseline ($p$<0.05). Approximately 20-30% reduction in IOP from the baseline was observed at 2$^{nd}$ follow up in all groups. The average degree of reduction was similar in LT and BT groups (29.2% and 27.9% respectively) while the least reduction was observed in DT group (20.3%). After 6 months of treatment (3$^{rd}$ follow up), the mean reduction of IOP from baseline was 7.83, 9.39 and 9.73 mm Hg in DT, BT and LT groups respectively, all considered statistically significant as compared to the baseline ($p$<0.05). At the end of the study period, all patients across 3 groups responded to the treatment. The average degree of reduction was, however, maximum in case of LT group (36.2%). A reduction of more than 30% of IOP from baseline was seen in 22 and 21 patients from LT and BT groups respectively while the same was observed in only 12 patients from DT group. Altogether around 90% of patients in our study responded with 21 to 36% reduction of IOP from baseline at the end on 6 months. There was no statistical significant difference in the IOP reduction between the three groups at the any of the three follow up visits.

**Table. 1:** Mean intraocular pressure (IOP) in three treatment groups at various time intervals (n=101).

| Groups | Intraocular pressure in mm Hg | | | |
|---|---|---|---|---|
| | Baseline | 1st follow up | 2nd follow up | 3rd follow up |
| DT (n=35) | 25.7 ± 4.25 | 23.04 ± 3.64* | 20.16 ± 3.67* | 17.85 ± 3.16* |
| BT (n=34) | 26.3 ± 5.86 | 21.3 ± 4.6* | 18.8 ± 4.6* | 17.9 ± 4.4* |
| LT (n=32) | 26.5 ± 4.76 | 21.23 ± 4.44* | 18.78 ± 4.8* | 16.8 ± 4.11* |

**Cup-disc ratio (CDR)**

The cup disc ratio, measured by indirect ophthalmoscopy, remained almost unaltered over 6 months in all the groups with the change being statistically insignificant ($p$>0.05).

**Adverse drug reactions**

Out of a total of 47 adverse drug reactions observed over 6 months of follow up, 21 were from the DT group, followed by BT (15) and LT (11). Dry mouth (14) in the DT group was the most common ADR and had probable causal relationship with the drug according to WHO-UMC and Naranjo's algorithm. Itching sensation in eyes was observed most frequently in BT group (7), with a possible causal relationship and in LT group, conjunctival hyperaemia (8) was the most commonly encountered ADR with a probable causal relationship. All ADRs were mild in severity, not warranting discontinuation of drug. Eight ADRs were observed to be preventable in nature.

## DISCUSSION

The present study aimed to evaluate the efficacy and safety of three drug combinations in the treatment of primary open angle glaucoma (POAG). A higher drop-out rate was seen which may be explained by the high cost of treatment (the drugs are out-of-pocket expense and not provided by the hospital) and the long duration of treatment. As ours is a Government institute, majority of the patients belong to lower socioeconomic group, hence the compliance may have been affected. The age of the patients ranged from 27-77 years and majority were in the 5th and 6th decade of their lives. The number of males was greater than females. All these demographic variables are on expected lines.

### *Efficacy*

A significant reduction ($p$<0.05) in the mean IOP level was seen with all three drug combinations as compared to baseline at 1, 3 and 6 months. The maximum reduction at the end of 6 months was seen in LT group (36.2%) and the minimum fall was observed in DT group (29.4%).

The mean IOP reduction with 2% dorzolamide and 0.5% timolol combination (DT group) in our study was 2.65 mm Hg at 1 month and 5.46 mm Hg at 3 months. This was less than what has been reported by Jothi *et al.*, 2010 and Nixon *et al.*, 2009. Decrease in IOP at the end of 6 months was least in this group and had the least number of patients with more than 30% reduction.

In a small (n = 30), single-blind, crossover trial, the mean reduction in morning peak IOP from baseline at 1 month was reported to be 7.8 mmHg with 0.1% brimonidine and 0.5% Timolol (Arcieri *et al*., 2007). This is somewhat more than what we observed (4.95 mm Hg at 1 month). A meta-analysis assessing the reduction in IOP by commonly used fixed combinations showed that brimonidine/timolol (BT) combination reduces the IOP level by 34.2% which was similar to our results (35.6%) (Cheng *et al*., 2012). In latanoprost and timolol (LT) group of our study, we observed a reduction of 7.72 mm Hg from baseline at 3 months, whereas others (Robert *et al*., 2011; Miglior *et al*., 2010) have shown a relatively higher reduction in mean IOP level. Garcıa-Sanchez et al. (2004) observed a mean IOP reduction of 9.5 mm Hg in the latanoprost/timolol group at 6 months which is quite similar to our findings (9.73 mm Hg). However, about 20% latanoprost/timolol treated patients achieved an IOP reduction of more than 15 mm Hg at 6 months in this study as compared to 47% in our study. Overall the 3 groups of our study showed a statistically significant decrease in IOP as compared to the baseline at the end of 6 months. When the three drug combinations were compared with respect to the reduction in IOP levels, LT and BT showed better response than DT, however no statistical significant difference was observed at any follow up. A meta-analysis assessing the IOP lowering effects of common fixed dose combinations in glaucoma has noted the same viz. that all lower IOP effectively with latanoprost/timolol combination achieving better response than brimonidine or dorzolamide with timolol (Cheng *et al*., 2012). We tried to assess the progression of disease by measuring CDR. There was, however, no statistically significant change in mean CDR over 6 months in any of the groups.

### *Safety*

In general, all three combinations were well tolerated and safe. No patient discontinued the treatment due to ADRs during the study period. Maximum number of ADRs (21) were observed in DT group with the dry mouth being commonest as has been observed in other studies (Jothi *et al*., 2010; Nixon *et al*., 2009). There were 15 ADRs in BT group, commonest being the itching sensation in eyes. Consistent with the results of previous studies (Diestelhorst *et al*., 2006; Ratol *et al*., 2012) the combination of timolol and latanoprost was commonly associated with conjunctival hyperaemia but was generally well tolerated.

As with any study, our work also has limitations. Compliance (considering that glaucoma is a chronic disease) and the cost effectiveness of the three combinations should also have been measured. At the same time, the high dropout rate, mainly due to lack of follow up but may also be due to the improvement or development of adverse reactions, could result in a skewed perception of our findings. To conclude, the present study suggests that all the three combinations are effective in treatment of primary

open angle glaucoma and none of them appears to be superior to the others. All combinations are well tolerated and do not give rise to any serious ADRs, necessitating discontinuation of therapy.

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