ABSTRACT

Background: Studies comparing the efficacy and tolerability of the three fixed combinations of timolol with its monotherapy are not readily available. In this background, the current prospective observational study was planned.

Aim and Objective: To evaluate and compare the intraocular pressure (IOP) reduction, change in visual field, and cup-disc ratio in glaucoma patients receiving timolol monotherapy vis-a-vis timolol based dual therapies among timolol sub-optimal responders.

Materials and Methods: After obtaining written informed consent and fulfilling the inclusion-exclusion criteria, fifty consecutive newly diagnosed cases of glaucoma or ocular hypertension with risk factors were recruited in the study. They received timolol eye drop up to 4th week. Participants not responding to timolol monotherapy optimally received either timolol plus brimonidine or timolol plus dorzolamide or timolol plus latanoprost for another 12 weeks. Participants responding optimally (at least 30% reduction of baseline) were continued with timolol monotherapy. Besides IOP changes, effects on visual field, visual acuity, cup disc ratio, safety, tolerability, and rate of persistency to therapy were studied.

Results: Fifteen participants (30%) achieved target IOP reduction at 4 weeks of timolol monotherapy. All four treatment groups achieved significant IOP reduction ($P < 0.001$) from baseline to 16th week. Participants receiving timolol followed by timolol plus latanoprost had shown the highest IOP reduction at 16th week both from baseline and 4th week value (ANOVA test, $P = 0.027$, $P = 0.000$ respectively). No change in visual field or visual acuity or cup disc ratio was noticed. Adverse drug reactions observed were mild and mostly self limiting.

Conclusion: Timolol and latanoprost combination might be a better choice in sub-optimal responders to timolol whereas it is wise to continue timolol monotherapy in optimally responders.

KEY WORDS: Glaucoma; Ocular Hypertension; Fixed Dose Combination; Anti-glaucoma Drugs; Timolol; Normal-Tension Glaucoma

INTRODUCTION

Glaucoma is a heterogeneous group of disorder marked by damage to the structural or functional integrity of the optic nerve that causes characteristic atrophic changes in the optic nerve resulting in vision loss. Glaucoma can be roughly divided into primary “open angle” (POAG) and “closed
angle” variety. Optic neuropathy can occur without an increase in intraocular pressure (IOP) (normal tension or low tension glaucoma) and some people maintain elevated IOP in the absence of nerve damage or visual field loss (ocular hypertensives), are considered at risk for glaucoma. With appropriate screening and treatment, glaucoma usually can be identified and its progress can be arrested before significant effects on vision occur. The exact cause of glaucomatous optic neuropathy is not known, although many risk factors have been identified, to include the following: elevated IOP, family history, race, age older than 40 years, and myopia. Although it is a multifactorial disease, lowering of IOP is the main focus in medical treatment of POAG, till today A rational pharmacotherapy should limit the number of medications in order to of glaucoma reduce the adverse effects. Most accepted principle is to start treatment with a single agent, assess after 4 weeks and if the response is not satisfactory the initial drug is either substituted or another drug is added.

Many fixed-dose combinations are now available containing either an alfa-agonist or prostaglandin analog or carbonic anhydrase inhibitor along with traditional beta-blockers. The clinical efficacy of such substances in lowering IOP has been shown in a number of studies. Nevertheless, the targets for IOP lowering are quite stringent and may not be reached using a single agent. In this case, the idea of combining two agents is an attractive one, particularly if they work by different mechanisms as is the case of above-mentioned combinations. Although fixed-dose combination treatments have been investigated earlier, studies comparing the efficacy and tolerability of the three above-mentioned fixed-dose combinations are not largely available. In the backdrop of paucity of knowledge, the current clinical study was conducted to assess the efficacy and tolerability of these widely used combinations as well as to compare the clinical outcome among suboptimal responders to timolol monotherapy.

The study was aimed to assess the clinical utility of timolol monotherapy in timolol responders (at least 30% reduction of IOP) and to compare the efficacy and safety of timolol containing fixed-dose combinations consisting either brimonidine (0.2%) or dorzolamide (2%) or latanoprost (0.005%) in suboptimal responders to timolol monotherapy. In addition, the persistency with the treatment had been assessed among the study population.

MATERIALS AND METHODS

The study had been conducted in collaboration with the department of pharmacology and department of ophthalmology at a tertiary care teaching hospital in rural West Bengal, India.

Approval from Institutional Ethics Committee was obtained prior to initiation of the study.

All consecutive newly diagnosed patients of open-angle glaucoma or ocular hypertension (OHT) with risk factors or normal-tension glaucoma attending the ophthalmology outpatient department (OPD) on every Monday and Thursday (2 OPD days/week) were recruited upon fulfilling the inclusion and exclusion criteria with requisite informed consent. The total period of study was 18 months from the enrollment of the first study subject to the completion of procedures of the last study subject. Each participant under the study was observed over a period of 16 weeks. The study was a comparative, uniocular, OPD-based prospective observational study. A purposive sample of 50 study subjects was initially recruited in the timolol monotherapy arm

Inclusion Criteria

Male or female, 18 years of age or above, newly diagnosed case of POAG or OHT (IOP > 21 mmHg) with risk factors (family history, diabetes, myopia, cup/disc ratio >0.6 in fellow eye, loss of vision in the fellow eye due to glaucoma) or normal-tension glaucoma, subjects able to understand the procedure, subjects able to provide informed consent.

Exclusion Criteria

Pregnant, breastfeeding mothers and women in reproductive age group without any birth control measures, uncontrolled systemic or psychiatric disease, known hypersensitivity to study medications, monoamine oxidase (MAO) inhibitor therapy, obstructive airway disease, cardiac conduction defect and cardiac failure, active ocular disease such as uveitis, ocular infections, severe dry eye syndrome and corneal abnormality, and intraocular surgery within the past 2 months.

Figure 1: Study flow-chart. T-timolol, T+L-timolol plus latanoprost, T+B-timolol plus brimonidine, T+D-timolol plus dorzolamide
At initial visit, all the patients attending ophthalmology OPD who fulfilled the study selection criteria were supplied with the informed consent document after detailing it to them. This initial visit was not regarded as the first visit.

After seven days, in the first visit (0 week) patients willing to participate were instructed to sign the informed consent form and were again checked for eligibility criteria. One vial of timolol maleate (0.5%) eye drop was dispensed to each eligible patient with instructions. They were asked to come for follow-up at 2 week intervals at 2nd (2nd week) and 3rd visit (4th week) for scheduled procedures [Table 1] and to return the empty vials of timolol eye drop at the 4th week visit. In this visit participants who achieved target IOP reduction (30% or more reduction of baseline IOP), named Gr1, were instructed to continue timolol therapy as directed and new vial was supplied. On the contrary, participants who had not achieved the target IOP reduction had been divided into three groups receiving latanoprost (0.005%) plus timolol (0.5%)-Gr2, brimonidine(0.2%) plus timolol(0.5%)-Gr3 and dorzolamide(2%) plus timolol(0.5%)-Gr4. This was done according to physician’s discretion. All the eye drops were supplied free of cost to the study participants. The scheduled procedures were performed and the participants were asked to come for follow-up after 8 weeks at the 4th visit (12th week) and again after 4 weeks for the 5th visit (16th week) with the supplied vials. In the 5th visit (16th week) participants were instructed to follow the prescription of the treating physician thereafter and to contact the principal investigator for any clarification. IOP was measured in each occasion at 10 AM to avoid diurnal variation.

Each ocular solution had to be used two drops twice daily in the study eye at 12 h interval.

**Study Parameters**

1. **Efficacy parameters**
   a. Reduction in IOP - IOP measured in all visits by applanation tonometry
   b. Change in Cup/disc ratio - measured by direct ophthalmoscope
   c. Change in visual field - measured using automated perimetry (Humphrey)
   d. Rate of persistence – number of patients persisted up to 16 weeks of treatment.

**RESULTS**

Statistical analysis was done through the statistical software (SPSS Inc. Chicago, IL version 21.0;), Microsoft Excell etc. All the statistical tests were interpreted at 5% significance level.

Total number of patients were 50 (Male-39 [78%] and Female 11 [22%]). The mean age of the patients was 66.02 ± 8.82 years.

**IOP Reduction**

Among enrolled study subjects (50), all completed the first 4 weeks of treatment with timolol monotherapy. A total of 15 participants (30%) achieved target level IOP reduction (timolol responders). They were continued with only timolol eye drop for another 12 weeks and one participant was lost to follow-up. Total suboptimal responders were thus 35 (70%). Among timolol responders, IOP reduction was statistically significant ($P < 0.0001$) at the 16th week from baseline with a mean reduction of 13.97, SD = 4.07. Thus, as single aniglaucoma agent, timolol reduced IOP significantly in participants who responded to it in the initial 4 weeks. In timolol - suboptimal-responders, while either using timolol plus latanoprost (Gr2), timolol plus brimonidine (Gr3),

<table>
<thead>
<tr>
<th>Study Visits</th>
<th>History, informed consent process</th>
<th>Checking selection criteria</th>
<th>IOP by applanation tonometry</th>
<th>Ophthalmoscopy (Direct and indirect) (For cup/disc ratio)</th>
<th>Automated perimetry (Humphrey visual field test)</th>
<th>Pulse and BP</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial visit</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Visit 1 (wk 0)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>Visit 2 (wk 2)</td>
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<td>X</td>
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<td>Visit 3 (wk 4)</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
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<td>X</td>
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<tr>
<td>Visit 4 (wk 12)</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Visit 5 (wk 16)</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
</tr>
</tbody>
</table>

Scheduled procedures are marked as (X) if performed.

Table 1: Schedule of study visits and procedures
or timolol plus dorzolamide (Gr4), all produce significant reduction of IOP from baseline ($P < 0.0001$) [Table 2]. To sum-up, in all four groups there was a statistically significant reduction of IOP from baseline to 16th week.

### Comparison between Four Treatment Groups

One Way ANOVA shows a significant difference in reduction of IOP from baseline to 16th week ($P = 0.027$) and the reduction was more in timolol plus latanoprost group [Table 3].

### Analysis between 4th week to 16th Week Value Among Four Treatment Groups

All of the four treatment groups showed significant ($P < 0.001$) reduction of IOP with a mean reduction of $3.21 \pm 1.67, 10.48 \pm 4.33, 7.75 \pm 3.07, 7.85 \pm 3.93$ in (Gr 1), (Gr 2), (Gr 3) and (Gr 4), respectively (Paired $t$-test mm Hg) [Table: 2].

Analysis regarding the comparison of IOP reduction (from 4th week to 16th week value) among four treatment groups showed significant statistical difference ($P < 0.001$), (One-way ANOVA). However, Gr2 (timolol plus latanoprost) showed a maximum reduction of IOP [Table 3]. That implies IOP reduction in timolol plus latanoprost treatment group was better than the other two groups.

### Change in Visual Acuity

There was no significant changes in visual acuity, visual field, or cup disk ratio in any patient at any visit from baseline value ($P > 0.05$).

### Adverse Drug Reaction

Stinging sensation was observed in all patient groups. timolol monotherapy had more chance of stinging sensation on eye than timolol plus latanoprost ($P = 0.001$, significant), timolol plus brimonidine ($P = 0.038$, significant) and timolol plus dorzolamide ($P = 0.630$, not significant), [Table 4].

Stinging sensations between other combination therapy groups (Gr2, Gr3, Gr4) were also not significant. Timolol monotherapy had less chance of transient blurring of vision than timolol plus dorzolamide ($P = 0.87$, not significant), other drugs did not cause transient blurring of vision.

### Safety and Tolerability

No antiglaucoma agent, either timolol or timolol plus latanoprost, timolol plus brimonidine combination, or timolol plus dorzolamide combination had a significant effect on MABP and heart rate of study subjects ($P > 0.05$).

### Table 2: Within group comparison of IOP at 16 weeks with baseline and 4 weeks value

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>Baseline IOP (Mean±SD) Range (Min-Max)</th>
<th>IOP at 4 weeks (Mean±SD) Range (Min-Max)</th>
<th>IOP at 16 weeks (Mean±SD) Range (Min-Max)</th>
<th>Sig. ($P$-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (Timolol monotherapy) $n=14$</td>
<td>29.51±5.94 (20.00–38.00)</td>
<td>18.75±3.58 (14.00–26.00)</td>
<td>15.54±2.79* (12.00–20.00)</td>
<td>0.000</td>
</tr>
<tr>
<td>Group 2 (Timolol plus Latanoprost) $n=15$</td>
<td>36.17±7.84 (22.00–46.00)</td>
<td>29.52±7.22 (16.00–40.00)</td>
<td>18.37±4.35† (12.00–28.00)</td>
<td>0.000</td>
</tr>
<tr>
<td>Group 3 (Timolol plus brimonidine) $n=9$</td>
<td>33.33±8.24 (20.00–44.00)</td>
<td>26.04±7.71 (14.40–38.00)</td>
<td>18.28±4.96† (11.60–26.00)</td>
<td>0.000</td>
</tr>
<tr>
<td>Group 4 (Timolol plus dorzolamide) $n=7$</td>
<td>33.28±8.42 (23.00–44.00)</td>
<td>27.42±7.63 (20.00–38.00)</td>
<td>21.00±6.50† (16.00–30.00)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

* $P<0.001$ in comparison to *Baseline IOP and †IOP at 4 weeks, within group paired $t$-test

### Table 3: Comparison of different treatment groups on mean IOP reduction

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>IOP reduction (baseline-16w) (Mean±SD) Range (Min-Max)</th>
<th>Sig. ($P$-value)</th>
<th>IOP reduction (4w-16w) (Mean±SD) Range (Min-Max)</th>
<th>Sig. ($P$-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timolol monotherapy (Gr1) $n=14$</td>
<td>13.97±4.07 (8.00–22.00)</td>
<td>0.027*</td>
<td>3.21±1.67 (2.00–6.00)</td>
<td>0.000*</td>
</tr>
<tr>
<td>Timolol plus Latanoprost (Gr2) $n=15$</td>
<td>17.80±4.79*</td>
<td>0.000</td>
<td>10.48±4.33</td>
<td>0.000</td>
</tr>
<tr>
<td>Timolol plus brimonidine (Gr3) $n=9$</td>
<td>15.04±4.10 (10.00–24.00)</td>
<td>0.000</td>
<td>7.75±3.07†</td>
<td>0.000</td>
</tr>
<tr>
<td>Timolol plus dorzolamide (Gr4) $n=7$</td>
<td>12.28±3.19 (7.00–16.00)</td>
<td>0.000</td>
<td>7.85±3.93</td>
<td>0.000</td>
</tr>
</tbody>
</table>

*Between groups (Gr1,Gr2,Gr3,Gr4) ANOVA test †$P<0.05$ in comparison to Gr 4, ‡$P<0.001$ and §$P<0.05$ in comparison to Gr1 (Post hoc Tukey’s test)
Rate of Persistence with Treatment

Overall rate of persistence with antiglaucoma drugs in this study in 16 weeks time frame was 90%. All study subjects (50) persisted in the initial timolol treatment phase (time frame 4 weeks). Five participants discontinued the treatment afterwards. One among timolol responders and one suboptimal responder did not continue the study beyond 4 weeks. Subsequently, one study participant discontinued in each of the Gr2, Gr3, and Gr 4 (rate of persistence in those groups was 88.8%) [Figure 1].

DISCUSSION

Reduction of elevated IOP is the only proven approach to protect against visual field loss in patients with open-angle glaucoma (OAG) or OHT, making ocular hypotensive agents critical to the management of these patients. If single-agent therapy is insufficient, a second hypotensive drug is added, which can produce an additional IOP decrease.[5] The 2-drug combination can be comprised of two individual agents or a fixed-combination (FDC) product. A systematic review confirmed that these two types of glaucoma therapies produce equivalent efficacy.[6] In a large study (n = 3333) of patients taking glaucoma medications, the majority (79%) reported that they were satisfied with their eye drops; however, nearly 1 in 10 patients (9%) were likely to have their medication changed at their next visit due to side effects.[7] Each hypotensive agent has a characteristic side effect profile, but FDC products as a group have a number of advantages over the Instillation of 2 individual drugs.[8] FDC is more convenient, avoid washout of the agents, which occurs when inadequate time is allowed between instillation of the first and second drugs, along with reduced lifetime exposure to preservative and better compliance due to reduced costs and less impact on quality of life.[9,10] IOP is also a factor that can be readily modified by pharmacological intervention.[11]

Different studies associate high IOP with visual field change and/or optic nerve damage and suggest that the onset of glaucoma is delayed and the severity reduced when IOP is reduced by treatment.[12,13] However, in the case of OHT with normal optic nerve heads and visual fields, the appropriate course is less clear. For lack of a precise indicator of future glaucomatous damage, it has been customary practice that patients with moderate IOP elevations be followed cautiously but the concept of treating elevated IOP prior to established glaucomatous damage has received considerable attention.[15] In several randomized, prospective studies of OHT between treatment and no treatment group, the treated eyes had a more favorable course with regard to glaucomatous damage.[16] IOP above 21 mmHg is usually taken as a cut-off level in the definition of OAG and OHT. Although it is a rough estimate, in the present study, it is taken as a reference, as mostly accepted.[17] To decide the target IOP, several regimens had been suggested: for minimal risk factors, lowering IOP by 20–30%; in moderate and multiple risk factors, lowering by 30–40% to prevent neuronal loss.[18] But to conduct a study we had to set a target IOP prefixed for all participants. It was decided to set as 30% of the baseline value after 1 month of therapy. The present clinical study was an uniocular study. Most authorities recommend a uniocular study of topical glaucoma medications which are intended for long-term use in order to assess patient-specific effectiveness and tolerability.[19,20] Using the untreated eye as a control is thought to remove variability due to diurnal fluctuation, operator technique, tonometer calibration, etc.[19,20]
study concluded that unioocular and binocular trials have similar predictive value when interpreted correctly.\[21\] Age older than 40 years is a risk factor for the development of POAG, with up to 15% of people affected by the seventh decade of life.\[1\] However, the disease itself is not limited to only middle-aged and elderly individuals. As a chance of OHT or established glaucoma in below 18 years is low, we enrolled participants only above 18 years. Topical beta-blocker therapy can be associated with severe bradycardia, arrhythmia, heart failure, syncope, and aggravation of bronchospasm and MAO inhibitors may interfere with the metabolism of brimonidine thus susceptible population were excluded from the study.\[22-25\] Pregnant women were excluded because of lack of enough evidence. Even though the use of the newer agents has expanded rapidly in many countries, timolol remains the most common first agent prescribed worldwide, it is cheap and cost-effective too.\[26\] IOP pressure is subjected to cyclic fluctuations throughout the day having peak in the morning.\[27\] So to minimize this error we had taken IOP at a particular time point (10 AM) in all patients in all visits. In the present clinical study, the mean age of the patient was 66.02 years which roughly corroborates with the mean age of glaucoma (60.54 years) in the population in India.\[28\] However, the difference of prevalence regarding sex is unclear.\[29\] In our study after initial 4 weeks of treatment, timolol monotherapy reduced IOP significantly (P < 0.0001), this finding corroborate with the finding of previously published study.\[30\] But in only 30% of cases target, IOP had been reached thus endorsing individualization of initial pharmacotherapy. In timolol responders, continued timolol monotherapy significantly reduced IOP at 16\textsuperscript{th} week from baseline and 4\textsuperscript{th} week value. In suboptimal responders to timolol monotherapy, there was a significant reduction of IOP at 16 weeks (in comparison to both from 4\textsuperscript{th} week and baseline value) in all dual therapy groups. But the study arm receiving timolol followed by timolol and latanoprost had shown better efficacy in terms of IOP reduction (both from baseline and 4\textsuperscript{th} week value) in comparison to all other treatment groups at 16\textsuperscript{th} week [Table 3]. A well-designed study with a larger sample size would be able to draw a conclusive evidence in the favor of this combination.

Patients who continued timolol as monotherapy up to the end of the study had shown significant IOP reduction from baseline. This information is agreed with the results of the previous studies.\[31\] Patients responded to timolol monotherapy in the first 4 weeks expected to maintain IOP in reduced level for long term. There is no improvement or deterioration of visual field, visual acuity, and cup disc ratio in any study arm. But in optimistic view, the progression of visual field loss was prevented in just 16 weeks of treatment. To comment on the reversibility of visual field a long-term study design is required. However, the finding in the study hints toward the irreversibility of visual field loss. That corroborates with the results of previous studies.\[30,32\] Persistence refers to the act of continuing the treatment for the prescribed duration. It may be defined as “the duration of time from initiation to discontinuation of therapy” (Joyce et al., 2008). This study had shown an optimistic view regarding the persistency with antiglaucoma medication which had been found to be low in several studies, varying from 20% to 64%.\[33\] But here overall rate of persistence with antiglaucoma medication was 90% within 4 months of time frame which might be a bit different in real-life scenario because of longer duration of therapy. The adverse events observed in the study were mostly confined to some ocular discomfort except very few systemic effects. Although ocular stinging sensation was observed with all agents, the chance was little bit more with timolol. Blurring of vision had been noted in patients treated with timolol and timolol plus dorzolamide combination. That implies that all the antiglaucoma agents were well tolerated. That was reflected by the good rate of persistence with glaucoma therapy in the study.

Despite of few limitations of the study like small sample size, not getting the diurnal variation of IOP, not determining the relationship between the study drug and all adverse events, lack of data on adherence to medication and cost-effectiveness of therapy, the main strength of the study is its design that simulates clearly the current approach of medical therapy in glaucoma.\[31\] It is among the very few clinical studies which can clarify our knowledge regarding the efficacy and tolerability of FDC as add-on therapy. It was a noble attempt to study all the efficacy parameters including visual field, visual acuity, and cup/disc ratio instead of focusing on IOP reduction only.

CONCLUSION

As anti-glaucoma regimen, the combination of timolol with either latanoprost, brimonidine, or dorzolamide could be a better choice in suboptimal responders to timolol therapy in terms of efficacy, safety, tolerability, and persistency whereas it is wise to continue timolol as monotherapy among optimally responders to it. Among combinations, timolol-latanoprost may have an edge over the others.

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