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ARTICLE INFO

ABSTRACT

Objectives: To evaluate safety and efficacy of Timolol and Brimolol (Brimonidine+Timolol) and study effect of aerobic exercise on intraocular tension (IOT) in timolol treated patients.

Methods: A prospective study including 90 cases of newly diagnosed primary open angle glaucoma (POAG) from ophthalmology inpatients, were divided into 3 groups: 1- Timolol, 2- Brimolol and 3- Timolol with Exercise. Each patient was administered with topical drugs followed up every 15th day for 1 month. Efficacy of drugs were tested based on IOT measurement by Non-contact tonometer and safety on the basis of ADR check list, fundoscopy and slit lamp examination. In group 2, patients were advised to do 30 min exercises.

Results: Mean reduction in IOT was statistically significant with values as 2.9, 7.8 & 5 mmHg and 6.1, 10.9 & 9.1 mmHg in group 1, 2 and 3 at 15th and 30th day respectively. Frequency of ADR in group 1, 2 & 3 was 36%, 40% & 30% respectively with the most frequent ADR in group 1 & 3 as burning of eyes (50%) & in group 2 as dryness (22%). Frequency of patients missing ophthalmic doses were 60%, 48% & 48% in group 1, 2 & 3 respectively with most frequent cause as ADR in group 1 & 3 and monetary reason in group 2. GQR-15 score was 35, 30.5 & 29 in group 1, 2 & 3.

Conclusion: Brimolol provides superior IOT lowering to timolol but is less well tolerated. Exercise along with timolol provides superior IOT lowering effect to timolol alone & is better tolerated, has superior visual quality of life with reduced frequency of missed ophthalmic doses.
INTRODUCTION:
Primary open angle glaucoma (POAG) is defined as a chronic and progressive disease, characterized by acquired loss of optic fibers, glaucomatous disc progression, visual field changes, and open angles in the absence of known underlying cause. Glaucoma is the second highest cause of blindness worldwide with an approximate half of glaucoma population ignorant about their disease. As per research estimates by 2020, 79.6 million people will be inflicted worldwide, of these, 74% will have POAG. In India, there are approximately 11.2 million persons aged 40 years and above diagnosed with glaucoma, out of which POAG is estimated to affect 6.48 million people.
To date we have proven therapy only for slowing glaucomatous visual field loss. The disease risk factor which can be modified is the intraocular pressure (IOP). Topical medications are often successful to lower IOP to an acceptable level. However, critical evaluation of safety and efficacy of IOP-lowering medications is utmost important as anti-glaucoma drugs are not equally effective in every patient. Furthermore, once initiated, IOP-lowering medications are often used throughout the lifetime of a patient. These drugs are quite expensive, may affect the quality of life, and may have adverse effects too. Therefore, it is incumbent on the clinician to make sure that medications have maximum ocular tolerability and effective IOP control thereby, preventing further visual field loss.
As an increasing number of people are becoming active in aerobic physical exercise such as jogging and bicycling, it would be interesting to identify any limitations/precautions or benefits concerning the effect of exercise on intra-ocular pressure. According to earlier few studies, all forms of physical exercise decrease IOP. However, the effect of exercise on the IOP of patients on anti-glaucoma medication has not been extensively studied.

From the results of the Ocular Hypertension Treatment Study, it was found that ocular hypertensive subjects with thinner central corneal thickness (CCT) are at increased risk of developing glaucoma. Various studies have indicated the effect of anti-glaucoma drugs on the mucoid layer of the tear film with inconsistent results. It decreases the production of tears resulting in dry eye. Hence, a correlation must be established between them.
Keeping all the outcomes of earlier studies pertinent to effective IOP control and anti-glaucoma drug related adverse effects present study was designed to evaluate and confirm the results of earlier studies in this regard with further extension to explore novel means of anti-glaucoma therapy for benefit of the patients.

MATERIALS AND METHODS:
This prospective comparative study included 90 cases of newly diagnosed open angle glaucoma patients with IOP between 25-30 mm Hg from ophthalmology inpatients (sample size calculated by using OpenEpi statistical software with 95% confidence level, 80% power). After getting approval from the Institutional Ethics Committee [Ref.SKNMC/ Ethics/App/228/2014] and written informed consent, Patients of either sex with an age range between 18 and 70yrs were be included in the study and divided into three groups depending on eye drops treatment they received as follows: (n=30)
Group 1: Timolol (BD)
Group 2: Timolol (BD) +Brimonidine (TDS)
Group 3: Timolol + Exercise (BD)
Patients with a baseline untreated IOP > 30mm Hg confirmed on 2 occasions within 1 week and with any ocular disease or surgery within the previous 3 months were excluded from the study.
A baseline physical and clinical examination of the patient was done at the time of enrolment. Each group of patients administered with the topical anti-glaucoma drugs and their combinations for one month were included and followed up once in 15 days. The allocation of the patients in group 1 and 2 was as per the Ophthalmologist prescription while in Timolol+ Exercise; it was according to simple
randomization as per 'Random table method' used in patient with Timolol administration. The efficacy of the drug was tested based on IOP measurement by non-contact tonometer, slit lamp examination and fundoscopy at interval of 15 days. The safety of the anti-glaucoma drugs and drug combination was tested on the basis of adverse drug reaction (ADR) check list, fundoscopy and slit lamp examination. In the exercise group of patients, they were advised to do 30 min exercise (jogging) every day for 1 month along with anti-glaucoma drug and all the above-mentioned examinations were performed at 15 days. In all the patients’ central corneal thickness (CCT), tear film break up time (TBUT), cup disc ratio (CDR) was measured at start, 15 days and at 1 month. The Naranjo's probability scale was used for causality assessment of adverse events. Each question could be answered positive (yes), negative (no), or unknown or not applicable (do not know). The ADR was assigned to a probability category from the total score as follows: definite ≥9, probable 5-8, possible 1-4, and doubtful ≤ 0. Severity of ADRs was assessed using Hartwig and Seigel scale and categorization was done as Mild= level 1 and 2, moderate= level 3 and 4 while severe= 5, 6 and 7.\(^{(9)}\)

**Statistical Analysis**

Efficacy analyses were performed for the study population (all patients randomized to treatment i.e group 3) with last observation carried forward (LOCF) for missing values and the per-protocol population (all patients with no major protocol violations) with no imputation for missing values. One-way ANOVA was used to compare the decrease in IOT values between the three groups followed by post-hoc tukey hsd test.

**RESULTS**

In this prospective comparative study, we have assessed and compared the efficacy and safety of various anti-glaucoma therapies in POAG patients. Total 90 patients enrolled in this study, 83 (92.2%) completed study; 5 (5.6%) patients discontinued owing to ADRs while 2 (2.2%) patients discontinued owing to the cost of treatment both of which were from Timolol + Brimonidine group. Patient demographic and socio-economic status is presented in table 1.

<table>
<thead>
<tr>
<th></th>
<th>Timolol</th>
<th>Timolol + Exercise</th>
<th>Timolol + Brimonidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (Range in yrs.)</td>
<td>53.2 (18-75)</td>
<td>51 (18-75)</td>
<td>46.86 (18-78)</td>
</tr>
<tr>
<td>Male (Female)</td>
<td>24(6)</td>
<td>23(7)</td>
<td>25(5)</td>
</tr>
<tr>
<td>Socio- Economic status</td>
<td></td>
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<td></td>
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<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Middle</td>
<td>13</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Lower</td>
<td>14</td>
<td>14</td>
<td>15</td>
</tr>
</tbody>
</table>

\(N=90,\) the socio-economic status of the patients was taken as per modified Kuppuswami classification\(^{(10)}\)

**Figure 1: Effect of Anti-Glaucoma Drug Therapies on IOP**
N=90, data analysis by two-way ANOVA followed by post hoc Turkey test; *p<0.05 compared to baseline and †p<0.05 when intergroup comparison was done. The mean fall in IOP from baseline was found significant (p<0.05) at 15 and 30 days follow up visit in all three groups. However this fall in IOP was found to be maximum in Timolol+ Brimonidine group (Group 2) with p<0.05, while minimal in Timolol group(Group 1) when intergroup comparison was made in each follow up visit (see figure 1). The number of patients reaching target IOP i.e. <20mm Hg at two follow up visits were 43% and 100% at respectively in Group 2. This was comparable in Timolol+ Exercise group (Group 3) with 30% and 75% patients respectively. While in Group 1 it was 20% and 60% during two follow up visits. Effect of anti-glaucoma agents on central corneal thickness (CCT), tear film break up time (TBUT), cup disc ratio (CDR) are presented in table 2. In Group 3, substantially reduced tear gland secretion was noted based on TBUT at second follow up visit but no such effect was observed in other treatment groups.

Among the patients who discontinued from the study, majority (70%) were owing to adverse events. ADR profile of anti-glaucoma agents with causality and severity assessment has been presented in figures 2A, 2B, 2C and 2D. The rate of discontinuations resulting from ADRs was comparable in the Timolol and the Timolol + Exercise group while lower in the Timolol + Brimonidine group (see figure 2B). Based on causality assessment, majority of the adverse drug reactions were in the probable category (i.e.15/45) only 7 out of 45 were of definite category.

ADR in Timolol + Brimonidine group (16 of 45, 35.5%) was comparable to the incidence in the Timolol group (18 of 45, 40 %) and higher than Timolol + Exercise group (11/45, 24.4%) as shown in figure 2B. There was one serious ADR reported in each group while 4, 2 and 1 moderate ADRs were reported in Timolol, Timolol + Brimonidine and Timolol + Exercise group respectively (see figure 2D). Based on data, the frequency of ADR was more common in elderly age group (60% vs. 40%) and was more associated with lower socio-economic status (65% vs. 35%).
Figure 2A. Overall Adverse Effects in Glaucoma Patients

The frequency of patients missing ophthalmic doses and the most frequent cause of missing ophthalmic doses are given in table 3. The GQR-15 (quality of life) score was 35, 29 & 30.5 in Group 1, 2 & 3 respectively. Quality of life score was higher in younger age group (<45 years) and was more associated in patients with upper lower socio-economic status.

Figure 2B: Adverse Events Associated with Anti-Glaucoma Treatment Among Groups

Figure 2C: ADRs Categorization of Anti-Glaucoma Agents on Naranjo’s Probability Scale
**DISCUSSION**

The efficacy and safety has varied depending on the anti-glaucoma medications. Effect of exercise on intra-ocular tension has been investigated in many previous studies but to best of our knowledge such a comparative study with existing anti-glaucoma treatment has never been researched before. All the individual parameters of the present study are discussed below in details.

The mean age in this study was 51 years with a male female ratio of 3:1 in contrast to majority of other studies where the overall mean age was more than 60 years with a lower male: female ratio <1.(11-13)

The results of this study show that the mean reduction in timolol group was 2.9 and 5.3 mmHg from baseline levels at 15 th and 30th day which was stastically significant while in another study, the mean reduction in IOT with the timolol group was 7.6 and 8.6 mmHg at 15 and 30 day respectively,(11) though both were statistically significant. In this study, the mean reduction in brimolol group was 7.8 from baseline at 15 th day while in other studies, it was 8 mmHg(12),5.9 mmHg(16) respectively. At 1 month, the mean reduction in brimolol group was 11.9 mmHg in the present study while in other studies, it was 3.97 mm Hg (16.81%)(12),3.9 mmHg (13), 7.6 mmHg (14), 6.2 mm Hg (15) respectively.

Overall, the frequency of ADR was 35% with the most common ADR as burning followed by dryness and blurring of vision. This finding was in disagreement to a similar study where the overall frequency of patients experiencing adverse events was (5 -7)%.(12) In this study, the frequency of ADR in Group 2 was 40% while in other studies, it was 54.8 % (16),53% (17) respectively. The frequency of ADR in Group 1 in the present study was 36 % while in a similar study,it was 40.8%. (17) In this study, the most common adverse event in Group 2 was dryness and burning of eyes (25% each) while in other studies, it was ocular burning (9.9%) and stinging (5.5%) (16), conjunctival allergy(17),burning (14) respectively.It was found that themost common adverse event in Group 1 in this study was burning of eyes (40%) followed by stinging (22%) while in a similar study, it was conjunctival allergy(17).

Hartwig severity scale was used to assess the severity of ADR’s in this study. The percentage of adverse events in mild-moderate category

![Figure 2D: ADRs Classification of Anti-Glaucoma Agents on Hartwig’s Severity Scale](image)
was 22% in monotherapy and 33.33% in combination therapy in contrast to a similar study with 76.5% and 78.5% respectively.\textsuperscript{(12)} There were very few serious adverse events among patients in all the groups (3.33%) in consistence with previously conducted study.\textsuperscript{(16)}

In this study, the overall adherence was 55% while in other studies, adherence to glaucoma pharmacotherapy among study participants was high with overall (71%)\textsuperscript{(18)} (86%)\textsuperscript{(16)} (71.9%)\textsuperscript{(17)} respectively. It is important to examine the reasons for study discontinuation in any clinical trial to ensure that a difference between groups in discontinuation rates does not confound the results. The reason for discontinuation in this study was ADR (70%) followed by monetary reason (30%) while in other studies, the reason for discontinuation was due to adverse drug reaction (50%)\textsuperscript{(16)}, adverse events (16.6%)\textsuperscript{(17)} respectively. In a particular study, the reasons for discontinuation were different with forgetfulness (62%) followed by lack of self-efficacy (59%)\textsuperscript{(19)}. If we discuss about individual groups, the adherence of patients in Group 2 was 48% while in other studies, it was 93.4%\textsuperscript{(13)}, (3.6%)\textsuperscript{(16)},11.0%\textsuperscript{(15)} respectively. The reasons for this difference maybe the fact that the quoted studies were conducted in developed countries.

In this study, patients with low socio-economic status were more commonly associated with low compliance based on the kuppuswami status (which includes education and income). In other studies, it was found that patients with lower health literacy were significantly less likely to express a problem with glaucoma medications side effects,\textsuperscript{(18,20-22)} respectively. Few studies explored lower income of patients with poor adherence to treatment\textsuperscript{(18,22,23)}.

In this study, it was found that higher age was associated with low adherence to the treatment with concurrent finding in other studies. Age-related conditions (especially elderly), whether physical or mental can adversely affect the ability of patients to adhere with their therapy. It may include poor administration technique, increased severity and frequency of ADR’s, poor economic condition.\textsuperscript{(22-24)}

In this study, smokers were two times more associated with non-compliance than non-smokers. this finding has been confirmed in another study where smokers were 2.9 times more likely to be noncompliant with a scheduled follow-up visit than those who did not smoke.\textsuperscript{(25)} It can be speculated that this relates to their general lack of concern for their health, as compared with non-smokers. The Kruskal Wallis test revealed that there was no difference in NEI-VFQ-25 scores due to age, gender, or type of glaucoma\textsuperscript{(26)} but this is the first study to our knowledge where the effect of drugs affecting the quality of life was assessed. In this study, the quality of life was highest in Group 3 owing to low side effects and cheaper treatment.

The reduction of IOP after exercise has been the subject of various investigations from a very long time. In normal subjects the intraocular pressure decreases during exercise, and its reduction is proportional to the work load. In this study, the intraocular pressure was significantly reduced when given with a β-blocker similar to the finding in a previous study.\textsuperscript{(5)} In another study, it was found that repeated aerobic exercise produces predictable physiologic changes which included improvements in the oxidative capacity of trained muscles and increased maximal oxygen uptake and cardiac output, along with lower heart rate and blood pressure at similar submaximal workloads.\textsuperscript{(27)}

Yoga is a traditional Indian system of exercises that is used for disease prevention and rehabilitation. Yoga ocular exercise is recommended by yoga practitioners for maintaining eye health. Results from this study indicate a significant decrease of IOP after yoga ocular exercise.\textsuperscript{(28)}

In this study, there was significant changes in cup: disc ratio and visual acuity concurring with previously conducted studies.\textsuperscript{(11,29)} CCT proved to be the most potent predictor for ocular hypertension subjects developing glaucoma, especially, with thinner corneas.\textsuperscript{(14,28)} Effect of brimonol on tear function was assessed in this study. Brimonidine group significantly reduced tear film break up time but it was unaffected in
other two groups. A previously conducted study had also a similar finding where the tear function tests of the patients after brimolol group was significantly reduced. (3)

To conclude, twice daily fixed Brimolol provides superior IOP lowering to Timolol monotherapy but it is less well tolerated and quite costly for the patients. Exercise along with Timolol provides superior IOP lowering effect in comparison with monotherapy of timolol & is better tolerated along with reduced frequency of missed ophthalmic doses. Brimolol substantially reduces tear gland secretion while timolol shows no such effect. Based on the present study, the results depict clinical significance of aerobic exercise as an additional treatment measure. Low compliance of the anti-glaucoma treatment due to high cost and adverse reactions is well known posing a major challenge before the clinicians. Combination of timolol and exercise provides a cheap, safe and good quality of life but with lower efficacy as compared to brimolol which will improve the compliance especially in patients of developing countries.

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