**COMPARISON OF INTRAOCULAR PRESSURE LOWERING EFFECT OF LATANOPROST AND TIMOLOL COMBINATION VERSUS LATANOPROST ALONE IN PRIMARY OPEN ANGLE GLAUCOMA**

Asad Jamal Dar, Ubaid Ullah Yasin*, Junaid Afzar Khan**, M uhammad Shahid*, Qamar Ul Islam*, Saad Mushtaq Malik***

Hameed Latif Hospital Lahore, *Armed Forces Institute of Ophthalmology Rawalpindi, **Combined Military Hospital Lahore, ***Combined Military Hospital Thal

**ABSTRACT**

Objective: To compare the intraocular pressure (IOP) lowering effect of topical drug combination (Latanoprost & Timolol) with Latanoprost alone in patients of Primary Open Angle Glaucoma (POAG).

Study Design: Randomized controlled Trials (RCT).


Patients and Methods: A total of 240 eyes of 120 patients (68 males and 52 females) were included in the study. The patients were randomized into two groups of 60 each using random numbers table. Group A (60 patients, 120 eyes) were put on topical drug combination of Latanoprost and Timolol eye drops and Group B (60 patients, 120 eyes) were treated with topical Latanoprost eye drops alone. IOP assessments were done at baseline, 2 weeks, 4 weeks and 8 weeks intervals after initiation of treatment.

Results: Both the groups were age matched with mean age in Group A was 56.39 ±8.50 years and in Group B was 55.61 ± 8.95 years (p=0.09). Both groups showed significant IOP decrease from the baseline at each follow up interval. However after 8 weeks of start of treatment, pressure lowering effect in group A (14.73 ± 2.50 mmHg) was significantly more as compared to Group B (9.10 ±2.51 mmHg) (p<0.001).

Conclusion: Combination therapy of Latanoprost and Timolol is more effective as compared to monotherapy with Latanoprost in lowering IOP of patients with POAG.

Keywords: Intraocular pressure, Latanoprost, Primary open angle glaucoma, Timolol.

**INTRODUCTION**

Glaucoma is the leading cause of irreversible blindness world wide. Timely diagnosis and treatment is important for disease management. Successful IOP control requires good patient compliance. In patients with POAG who do not achieve their target intraocular pressure (IOP) level with single ocular pressure lowering agent, addition of another medication is recommended by European Glaucoma society. In fact, most of the patients have to use more than one ocular hypotensive drugs to reduce IOP to levels that can halt disease progression. For these cases, a combination therapy may be preferred for good patient compliance and adequate disease control. Ocular hypotensive agents that offer once daily dosing such as prostaglandin analogues may enhance patients compliance compared with more complex drug combinations. Latanoprost and Timolol have different mechanisms of action. Latanoprost which is a prostaglandin F2 alpha analogue acts primarily by increasing aqueous outflow facility through uveoscleral route, whereas Timolol which is a non selective beta blocker reduces IOP by decreasing production of aqueous humor. The combination of these two drugs has an additive IOP lowering effect. Our study will help to prescribe best possible drugs for management of POAG.

**PATIENTS AND METHODS**

These randomized clinical trials were conducted at Armed Forces Institute of Ophthalmology (AFIO) Rawalpindi from Dec...
2009 to May 2011. Approval of the Ethical Committee was obtained prior to the start of study. The research was conducted according to the ethical standards established by the Helsinki Declaration. A written informed consent was obtained from all the patients.

The subjects were serving as well as retired defense personnel, their families and civilian patients. The patients included in the study were those of primary open-angle glaucoma with an IOP in the range of 20 mmHg to 36 mm Hg. Following patients excluded from the study:

- Angle closure glaucoma
- Any ocular filtering intervention i.e., surgical or laser.
- Use of a systemic medication known to affect IOP levels like β-adrenergic antagonists
- Any secondary glaucoma.
- Patients of bronchial asthma and Chronic Obstructive Pulmonary Disorders (COPD).

**Data Collection Procedure**

At screening; detailed ophthalmic and medical history, best corrected visual acuity, ophthalmic evaluation including cup disc ratio, gonioscopy and IOP measurement with a calibrated Goldman Applanation Tonometer (GAT) in both eyes were carried out. The study included 120 patients randomly divided into two equal groups by random numbers table.

Group A: Patients assigned combination therapy instilled 1 drop in the eye in the evening of Xalacom Eye Drops (0.005% Latanoprost and 0.5% Timolol maleate) marketed by Park Davis/ Pfizer

Group B: Patients to receive monotherapy with Latanoprost, administered 1 drop in the evening of Latep eye drops (0.005% Latanoprost) marketed by Schazoo laboratories.

Adverse effects of both the topical drugs like redness of eyes, corneal punctate epithelial erosions, reduced aqueous tear secretion, foreign body sensation, eye lash lengthening, iris hyperpigmentation and cystoid macular oedema were explained to patients. All adverse effects were monitored throughout the study. The follow up of all adverse events was done until they resolved or stabilized but none resulted in discontinuation of treatment. The patients from Pakistan Armed Forces were entitled for free medicines.

At each follow up visit i.e. 2 weeks, 4 weeks and 8 weeks, the IOP was measured in both eyes using the calibrated GAT. The IOP was taken between 0900 hours and 1200 hours on each visit so that the phenomenon of diurnal variation of IOP can be minimized. All the findings including demographic details, ocular examination findings, pre and post treatment IOP readings and adverse effects of treatment were recorded on a pre designed proforma. Four patients (8 eyes) in combination drug group and five patients (10 eyes) in Latanoprost group didn’t complete the study and they were excluded from study. The analysis of primary efficacy was based on assessments of mean IOP at 2 weeks, 4 weeks and at 8 weeks.

**Data analysis**

Data analysis was done by using SPSS version 15.0. To describe the data, descriptive statistics were used. Chi-square test was used to compare gender between both the groups. Paired sample t-test was used to compare IOP within both experimental groups. Independent sample t-test was used to compare the age and decrease in IOP between the groups. p-value < 0.05 was considered as significant.

**RESULTS**

The mean age of the patients in group A was 56.39 ± 8.50 years and in group B was 55.61 ± 8.95 years (p = 0.090) (Fig-1). Overall male to female ratio was 1.3:1. The group A included 36 (60%) males and 24 (40%) females whereas group B composed of 32 (53.3%) males and 28 (46.6%) females (p = 0.46). The base line (pre treatment) IOP in group A was 29.29 ± 3.25mmHg and group B was 28.67 ± 3.37mmHg (p = 0.17). After two weeks of starting therapy, IOP decreased in both groups (Fig-2). This IOP lowering effect persisted at various time intervals of follow up (Table-1). In group A, baseline mean IOP reduced to 14.85 ± 2.15 mmHg after treatment at 8th week of follow up (p<0.001) while in group B, baseline
mean IOP reduced to 19.26 ± 2.95 mmHg (p<0.001) (Table-2). Mean IOP decrease over 8 weeks from base line in group A was 14.73 ± 2.50 mmHg and in group B was 9.10 ± 2.51 mmHg (p<0.001) (Table-2).

Both therapies were safe and well tolerated. However 14.2% (8 out of 56) participants in the group A and 16.3% (9 out of 55) in the group B reported conjunctival hyperemia (p=0.76).

**DISCUSSION**

Glaucoma is the leading cause of irreversible blindness worldwide. Timely medical therapy has been found to be the most appropriate management for disease control and progression. However patient compliance has always remained a problem in achieving this goal. Reducing the number of times the patient has to use medicine daily along with the use of a single bottle instead of many is handier for the patients. It has shown much better results when compared to more complex regimens which are to be instilled many times a day too\[14\].

Our study demonstrated that both the combination therapy as well as monotherapy with the Latanoprost, significantly reduced IOP from pretreatment levels. Our results are comparable to other studies that have been done locally and internationally. A local study conducted by Hussain I et al, showed Latanoprost reduced IOP by 27% at 4th week, 30% at 8th week and 33% at 12th week\[15\]. A nother local study conducted by Tayyib M et al, also showed almost the same results\[16\]. A study conducted by Qureshi NA showed that there was 30% (7.88 mmHg) mean reduction in IOP with Latanoprost\[17\]. Local data on the efficacy of

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**Table-1: Intraocular pressure (IOP) comparison at various time intervals.**

<table>
<thead>
<tr>
<th>Visits</th>
<th>Mean IOP (mmHg) ± SD (95% Confidence Interval)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (n=112)</td>
<td>Group B (n=110)</td>
<td></td>
</tr>
<tr>
<td>Base line</td>
<td>29.29 ± 3.25 (28.69-29.89)</td>
<td>28.67 ± 3.37 (28.04-29.3)</td>
</tr>
<tr>
<td>2 Weeks</td>
<td>19.59 ± 3.32 (18.98-20.2)</td>
<td>22.35 ± 3.37 (21.72-22.98)</td>
</tr>
<tr>
<td>4 Weeks</td>
<td>17.37 ± 2.68 (16.87-17.87)</td>
<td>20.38 ± 3.30 (19.8-20.96)</td>
</tr>
<tr>
<td>8 Weeks</td>
<td>14.85 ± 2.15 (14.45-15.25)</td>
<td>19.26 ± 2.95 (18.71-19.81)</td>
</tr>
</tbody>
</table>

**Table-2: Intraocular pressure (IOP) reduction at various time intervals from baseline.**

<table>
<thead>
<tr>
<th>Visits</th>
<th>Mean IOP Reduction (mmHg) ± SD (Percent decrease)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>Group B</td>
<td></td>
</tr>
<tr>
<td>2 Weeks</td>
<td>9.97 ± 2.10 (34.03%)</td>
<td>6.00 ± 1.71 (20.92%)</td>
</tr>
<tr>
<td>4 Weeks</td>
<td>12.20 ± 2.47 (41.65%)</td>
<td>7.98 ± 1.93 (27.83%)</td>
</tr>
<tr>
<td>8 Weeks</td>
<td>14.73 ± 2.50 (50.29%)</td>
<td>9.10 ± 2.51 (31.74%)</td>
</tr>
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</table>
combination of Latanoprost and Timolol was not available however few local studies on combination of Dorzolamide and Timolol have revealed a reduction of IOP by 27-30% which is almost equal to that achieved with Latanoprost alone. The present study found that patients treated with fixed combination therapy (Latanoprost and Timolol) had a 50% reduction in IOP compared with baseline levels, which was significantly greater than that achieved with the Latanoprost alone 32% (p<0.001).

Our results for reduction in IOP with combination therapy and Latanoprost alone are also comparable to international studies. A study conducted by Konstas AGP et al in Greece compared fixed combination of Latanoprost and Timolol with Latanoprost alone. The baseline untreated mean IOP in the study was 24.2 ± 2.0 mmHg. The IOP reduced to 19.2 ± 2.6 mmHg in Latanoprost group and 16.7 ± 2.1 mmHg in the combination therapy group which is statistically significant (p < 0.001).20

Another study conducted by Higginbotham EJ et al studied the comparison of combination therapy (Latanoprost and Timolol) with each Latanoprost and Timolol alone. The intraocular pressure levels prior to start of treatment were similar; however at week 26, in the combination therapy group they were 19.9 ± 3.4 mmHg, in Latanoprost treated group 20.8 ± 4.6 mmHg, and in Timolol treated patients 23.4 ± 5.4 mmHg. The mean reduction from pre treatment IOP levels was greater among patients receiving combination therapy compared with monotherapy group (p < 0.001).14

As from the results of previous studies both therapies were safe and well tolerated. The most common adverse event associated with prostaglandin use was hyperemia, 13 occurred in both treatment groups. The advantages of a combination drug to treat patients of glaucoma include convenience, compliance and cost effectiveness. Multiple separate medications have been associated with poorer patient compliance, 22-25 suggesting that those patients who are treated with a fixed combination therapy are more adherent to the treatment.

**CONCLUSION**

Fixed combination of Timolol and Latanoprost is more effective in achieving proper control of IOP levels as compared to Latanoprost alone in patients of POAG. The combination drug therapy should be considered whenever more than one drug is required to achieve the desired IOP.

**Conflict of Interest**

This study has no conflict of interest to declare by any author.

**REFERENCES**


