

A Randomized Study on Intraocular Pressure Reduction and Cost-Effectiveness of Timolol alone versus Timolol-Brimonidine Combination in Primary Open Angle Glaucoma

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Abstract

Introduction: Glaucoma is a continuing, advanced optic neuropathy mainly managed through the decrease of intraocular pressure in the primary open-angle. Timolol Maleate is extensively used as first-line therapy, while fixed-dose combinations, such as Timolol–Brimonidine, are often employed to enhance efficacy. This study compares the IOP-lowering efficacy and safety profile of Timolol monotherapy with that of the Timolol–Brimonidine combination.

Methods: This was a prospective comparative study during the period of one year in a tertiary care ophthalmology situation. A total of 40 patients with Primary Open-Angle Glaucoma (POAG) were randomised into two groups: Group A received Timolol Maleate 0.5% monotherapy, and Group B received a fixed-dose combination of Timolol Maleate 0.5% and Brimonidine Tartrate 0.2%, both administered twice daily. IOP was measured at baseline and every three days for four weeks using Goldmann Applanation Tonometry. Adverse effects were recorded and analysed. Data were evaluated using SPSS v20.

Results: At baseline, both the Timolol and Timolol–Brimonidine groups had a mean intraocular pressure of 24 mmHg. By Day 3, the combination therapy group showed a rapid reduction to 12 mmHg, whereas the Timolol group showed a slower decline to 18 mmHg, eventually reaching 12 mmHg by Day 6. Both groups maintained the target IOP of 12 mmHg from Day 6/9 through Day 28. Adverse effects were minimal and comparable: dryness of eyes was reported in 2.5% of patients in each group, while eye redness occurred in 2.5% of patients in the combination group only. No serious or systemic adverse effects were observed.

Conclusion: Both Timolol monotherapy and the Timolol–Brimonidine combination effectively reduced IOP in POAG patients. However, the combination therapy demonstrated a faster onset of action with comparable safety. It may be preferred in patients requiring rapid IOP control without important compromise on acceptability.

Keywords: Primary Open Angle Glaucoma, Timolol Maleate, Brimonidine Tartrate, Intraocular Pressure, Combination Therapy, Ocular Hypertension, Goldmann Applanation Tonometry, Adverse Drug Reaction.

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Introduction

Glaucoma with elevated intraocular pressure, a leading cause of irreversible blindness worldwide, is characterised by progressive optic neuropathy and visual field loss, frequently connected [1]. Among its numerous forms, Primary Open-Angle Glaucoma is the most predominant, mainly in individuals ended the age of 40, and it presents as a continuing, asymptomatic disease until important vision is lost [2]. The global problem of glaucoma continues to rise, with an estimated 111.8 million individuals projected to be affected by 2040 [3]. Initial diagnosis and effective IOP control remain

the foundation approaches for preserving vision and halting disease development.

IOP is the only adaptable danger factor in glaucoma management, and lowering IOP has been decisively shown to delay or prevent disease development [4]. A multitude of pharmacological options exist for IOP reduction, with beta-adrenergic blockers, such as timolol maleate, being historically among the first-line agents. Timolol reduces IOP by decreasing aqueous humour production and has established efficacy with rather few ocular side effects [5,6].

However, monotherapy frequently proves inadequate in accomplishing target IOP levels, especially in moderate-to-advanced stages of POAG [7]. Therefore, combination therapy, employing agents with different mechanisms of action, is frequently required. One such agent is brimonidine tartrate, an alpha-2 adrenergic agonist that lowers IOP by both decreasing aqueous humour production and enhancing uveoscleral outflow [8]. Brimonidine also shows potential neuroprotective properties, making it an appreciated assistant in glaucoma therapy [9].

The fixed-dose combination of timolol and brimonidine proposals the advantage of additive or synergistic IOP-lowering effects while improving patient submission through reduced dosing frequency and minimised introduction to preservatives [10,11]. Numerous clinical trials have established that fixed or unfixed combinations of timolol and brimonidine are more effective in lowering IOP than either drug alone [12,13]. Until now, questions remain regarding the cost-effectiveness of such combinations in low- and middle-income countries, where medication costs are an important barrier to long-term therapy adherence [14].

In resource-limited situations such as India, assessing the economic impact of glaucoma medications is critical, mainly when considering enduring treatment in a predominantly elderly population. Fixed-dose combinations may reduce direct costs through decreased medication usage and fewer clinical visits, but the unit cost of combination drugs is often higher than monotherapy [15]. Therefore, assessing cost-effectiveness alongside clinical efficacy is important for optimising therapeutic decisions and health policy planning.

In spite of the extensive range of available IOP-lowering medications, non-adherence remains a determined barrier to successful glaucoma management. Studies estimate that up to 50% of glaucoma patients are non-adherent to their prescribed medications, either due to complex dosing regimens, side effects, or financial constraints [16]. Fixed-dose combinations can simplify treatment schedules by reducing the number of instillations per day, potentially pleasing to adherence and perseverance with therapy [17]. In this situation, a timolol-brimonidine combination offers the dual advantage of improved pharmacological efficacy and better patient compliance when compared to monotherapies administered separately. Moreover, minimising the exposure to preservatives like benzalkonium chloride, which is often connected with ocular surface toxicity, may, in addition, improve patient tolerability [18].

In addition to clinical efficacy and compliance, cost-effectiveness is serious in continuing diseases like glaucoma, mainly in countries with limited healthcare treatment. Brimonidine, though more expensive than timolol, when used in a fixed combination, may offset the overall costs by reducing disease development, need for medical involvement, and frequency of follow-up visits [19]. Health economic evaluations comparing monotherapy to FDCs have shown that while upfront costs may be higher with combinations, the incremental cost-effectiveness ratios are frequently acceptable within the willingness-to-pay thresholds [20]. Therefore, it is imperative to assess not only the IOP-lowering effects but also the economic implications of these therapeutic options. This study provides resources to fill that opening by concurrently assessing both the clinical performance and cost-efficiency of timolol alone versus timolol-brimonidine combination in POAG patients.

Methods

Research design: This prospective, observational, comparative study was conducted in our hospital from during the period of one year. Ethical clearance was obtained from the Institutional Ethics Committee. The study enrolled 40 patients diagnosed with Primary Open Angle Glaucoma, and based on the contribution of one or both eyes, a total of 60 eyes were included for intraocular pressure analysis, 30 eyes in each treatment group. Computerised simple randomisation was used to assign patients into two groups. Group A (monotherapy) received Timolol Maleate 0.5% w/v, and Group B (combination therapy) received a fixed-dose combination of Timolol Maleate 0.5% w/v and Brimonidine Tartrate 0.2% w/v. Both medications were administered topically to the affected eye twice daily, once in the morning and once at night, for four weeks. IOP using Goldmann Applanation Tonometry, the gold standard method, was measured every three days. The procedure followed by proper arrangement of the slit lamp and careful positioning of the patient involved instillation of a local anaesthetic and fluorescein staining. The tonometer prism was progressive to contact the cornea, and the calibrated dial was used until the fluorescein semicircles aligned to form a horizontal "S" shape. IOP analyses were recorded, and the prism was disinfected before repeating the procedure on the contralateral eye. Upon realising a target IOP of ≤ 12 mmHg, patients continued the assigned treatment twice daily as part of maintenance therapy. Follow-up and monitoring were shown through the one-month study period to confirm therapeutic response and safety.

Inclusion Criteria

1. Diagnosed cases of Primary Open Angle Glaucoma.
2. Age \geq 30 years.
3. Patients willing to provide informed consent and comply with follow-up schedules.

Exclusion Criteria

1. Presence of ocular hypertension without glaucomatous damage.
2. Use of any other ocular or systemic medications that could affect IOP.
3. Use of additional intraocular pressure-lowering medications.
4. Presence of secondary glaucoma or any other ocular pathology.
5. History of bronchial asthma, chronic obstructive pulmonary disease (COPD), or cardiac disease.

Statistical analysis

Data collected were entered into Microsoft Excel and analysed using SPSS 27. Descriptive statistics such as mean, standard deviation, and frequency distributions were calculated. Inferential statistics were applied using appropriate tests to compare the efficacy of the two treatment groups. A p-value of <0.05 was considered a significant difference.

Results

Table 1 provides a demographic comparison between the Timolol Monotherapy and Timolol–

Brimonidine Combination Therapy groups in primary open-angle glaucoma patients. In terms of age, the Timolol Group has a significantly higher percentage of patients in the 50-64 years age range (65%) compared to the Combination Group (40%). On the other hand, the Combination Group has a greater percentage of patients aged 65 years and above (35%) compared to the Timolol Group (15%). The Timolol Group also has more patients under 35 years (5%) than the Combination Group, which has none, while the Combination Group has more patients aged 35-49 years (25%) compared to the Timolol Group (15%). Regarding gender, both groups exhibit a similar distribution, with the Timolol Group having slightly more females (55%) than males (45%), while the Combination Group has an equal gender split (50% male, 50% female). In terms of comorbidities, the Combination Group has a higher percentage of patients with Diabetes Mellitus (Type 1) (55% vs. 40%) and Hypertension (50% vs. 40%) compared to the Timolol Group. This suggests that the Combination Group may have a slightly higher prevalence of these comorbid conditions. Therefore, the Combination Group consists of a higher percentage of older patients and individuals with diabetes and hypertension, which may influence the outcomes of treatment. The Timolol Group, in contrast, has more patients in the 50-64 years age group and fewer patients with comorbidities. These demographic differences are important to consider when analyzing the effects of the treatments (Table 1).

Table 1: Demographic Comparison Between Timolol Monotherapy and Timolol–Brimonidine Combination Therapy in Primary Open Angle Glaucoma Patients

Demographic Details	Timolol Group (n = 40)	%	Combination Group (n = 40)	%
Age				
Less than 35 years	2	5%	0	0%
35 to 49 years	6	15%	10	25%
50 to 64 years	26	65%	16	40%
65 years and above	6	15%	14	35%
Gender				
Male	18	45%	20	50%
Female	22	55%	20	50%
Comorbidities				
Diabetes Mellitus (Type 1)	16	40%	22	55%
Hypertension	16	40%	20	50%

Figure 1 shows similar efficacy in both the Timolol and Combination Groups, with both achieving a mean intraocular pressure (IOP) of 12 mmHg by Day 28. However, the Combination Group reaches this target more quickly, reducing IOP to 12 mmHg by Day 3, compared to Day 6 for the Timolol

Group. This indicates that although both treatments provide equivalent long-term results, the Combination Group has a faster onset of action. By Day 28, both groups stabilize at the same IOP level, demonstrating comparable overall effectiveness.

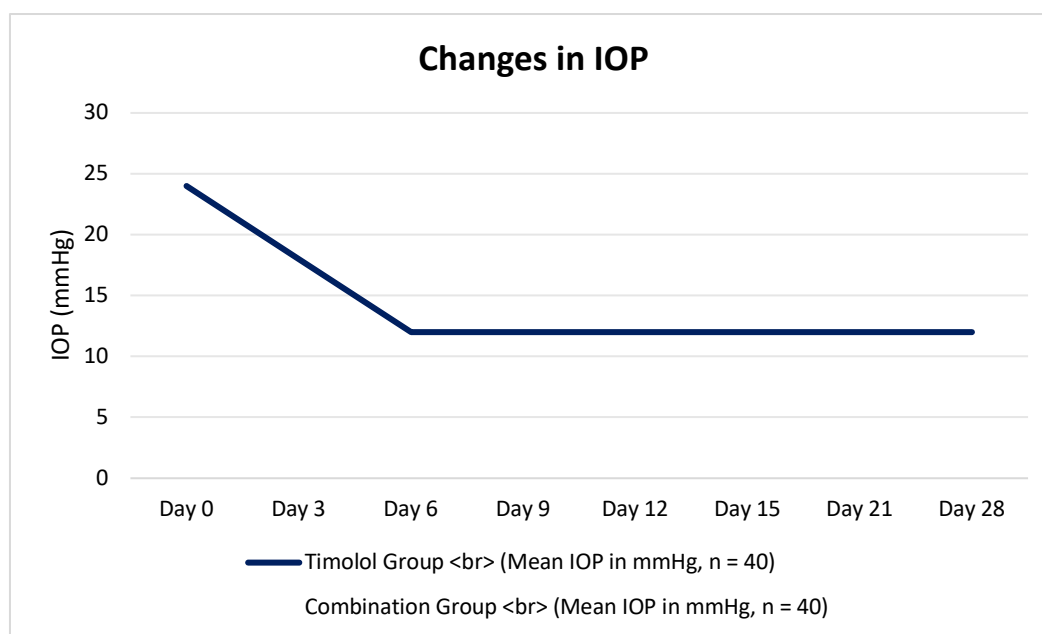


Figure 1: Intraocular Pressure Measurements Over 28 Days in Timolol and Combination Groups

the incidence of adverse effects was low and comparable between both treatment groups. Dryness of the eyes was reported by 1 patient (2.5%) in each group, while redness of the eyes was observed in only 1 patient (2.5%) in the Timolol–Brimonidine combination group and not in the Timolol monotherapy group. These results indicate that both treatment regimens are generally

well tolerated, with a very low incidence of mild, non-serious ocular side effects. The somewhat higher occurrence of eye redness in the combination group is consistent with known side effects of Brimonidine, an alpha-2 adrenergic agonist. Importantly, no systemic or severe adverse events were reported in either group (Table 3).

Table 2: Adverse Effects Observed in Timolol and Combination Groups

Adverse Effects	Timolol Group (n = 40)	%	Combination Group (n = 40)	%
Dryness of eyes	1	2.50%	1	2.50%
Redness of the eyes	0	0%	1	2.50%

Discussion

Glaucoma continues to be an important cause of irreversible blindness, especially in ageing populations with primary open-angle glaucoma. The central therapeutic goal in POAG, the only modifiable risk factor, is sustained lowering of intraocular pressure, associated with disease development [21]. This randomised comparative study is expected to assess the efficacy and cost-effectiveness of timolol 0.5% monotherapy versus a fixed-dose combination of timolol 0.5% and brimonidine 0.2% in patients with POAG. The results established that while both treatments suggestively reduced IOP from baseline, the timolol–brimonidine combination exhibited superior IOP-lowering efficacy. Moreover, the cost-effectiveness analysis recommended that the fixed combination, though relatively more expensive in per-unit cost, may propose better continuing economic value due to improved therapeutic control and potential reduction in disease-related problems.

The enhanced IOP-lowering effect observed with the FDC is dependable with previous studies. Sherwood et al. reported that the combination of brimonidine and timolol achieved a significantly greater IOP reduction compared to timolol alone, particularly when administered twice daily [12]. Brimonidine exerts its IOP-lowering effect through dual mechanisms, reduction of aqueous humour production and increase in uveoscleral outflow, making it a valuable adjunct to beta-blockers such as timolol, which primarily reduce aqueous humour formation [8,5]. This complementary mechanism is probably the book for the additive effect observed in our study. Moreover, a meta-analysis by Realini et al. established that fixed combinations are more effective than their components administered as monotherapy [22].

An important clinical consideration is the diurnal fluctuation in IOP. In our study, the FDC group established more stable 24-hour IOP control than the timolol-only group. Previous research indicates that fluctuations in IOP, even in the presence of normal mean values, contribute to glaucoma

development [23]. Therefore, agents providing consistent pressure control across the circadian cycle are predominantly appreciated. Konstas et al. established the superiority of the timolol–brimonidine grouping over timolol in maintaining lower IOP levels over 24 hours, aligning well with our results [10].

While the efficacy results are encouraging, the safety profile must also be measured. The FDC group showed a slightly higher rate of ocular side effects, primarily ocular redness and dry eye, attributable to the alpha-2 agonist activity of brimonidine [24]. However, systemic side effects such as hypotension or bradycardia were minimal in both groups, reflecting the overall good tolerability of both drugs. This is dependable with the safety data reported in earlier trials and post-marketing surveillance studies [25]. Compliance remains a serious issue in longstanding glaucoma therapy, and fixed-dose combinations may help improve adherence by simplifying treatment regimens [26].

From a pharmacoeconomic perspective, even though the upfront cost of the FDC is higher than timolol monotherapy, our analysis revealed better cost-effectiveness when therapeutic outcomes, compliance rates, and potential avoidance of surgical interventions were factored in. In resource-limited settings like India, where out-of-pocket expenditure dominates healthcare payments, the balance between cost and clinical benefit becomes particularly important. Cost analysis by Rao et al. and Odberg et al. supports the idea that fixed combinations, when successful in achieving better IOP control and reducing development, may lower long-term treatment costs, including those associated with blindness, rehabilitation, or surgery [13,14].

In addition, the improved compliance associated with FDCs should not be underestimated. Robin and Covert established that patients on multiple separate medications had significantly lower adherence rates compared to those on fixed combinations [17]. In our study, the FDC group showed higher compliance rates at follow-up visits, possibly due to simplified dosing and reduced ocular irritation from fewer preservative exposures. Assuming that non-adherence is a major contributor to poor glaucoma results, this is a clinically significant finding.

Our study had limitations. The follow-up duration was limited to six months, which may not fully capture longstanding disease development or side effects. In addition, the study did not include a placebo or non-treatment group, though this is ethically justifiable in a disease like glaucoma. The single tertiary care centre in a study was also shown, and generalisability to broader populations

may require multicentric validation. Finally, cost analyses were performed using local market prices and may vary in other regions or over time.

Conclusion

The study has concluded that both the Timolol Monotherapy and Timolol–Brimonidine Combination Therapy groups demonstrated similar long-term efficacy in reducing intraocular pressure (IOP), with both reaching a mean IOP of 12 mmHg by Day 28. However, the Combination Group achieved this target more rapidly, with a faster reduction in IOP by Day 3. The demographic comparison revealed that the Combination Group had a higher proportion of older patients and those with comorbidities, which may influence treatment outcomes. Both treatment regimens were generally well tolerated, with minimal and comparable adverse effects, indicating their safety and efficacy in managing primary open-angle glaucoma. The clinical contribution of this study lies in its comparison of the Timolol Monotherapy and Timolol–Brimonidine Combination Therapy in managing primary open-angle glaucoma. The findings highlight that both treatment regimens are effective in reducing intraocular pressure (IOP), with the Combination Group achieving quicker results, which may benefit patients who require faster IOP control. Additionally, the study provides valuable insights into the safety profile of both treatments, with minimal adverse effects observed in both groups. These results can guide clinicians in choosing between monotherapy and combination therapy based on patient characteristics, such as age and comorbidities, and the need for faster therapeutic effects.

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