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To Compare the Effect of Fixed-Drug Combinations of Brimonidine+Timolol and Ripasudil+Timolol in Glaucoma

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Background: Glaucoma is a chronic, progressive optic neuropathy and a leading cause of irreversible blindness worldwide. Reduction of intraocular pressure (IOP) remains the only proven strategy to slow disease progression. Fixed-drug combinations are commonly used to enhance IOP control and improve treatment adherence. While Brimonidine + Timolol is an established combination, comparative data with newer combinations such as Ripasudil + Timolol, particularly in the Indian population, remain limited.

Materials and Methods: This prospective, randomized, hospital-based interventional study was conducted in the Department of Ophthalmology at a tertiary care centre in North India. Ninety newly diagnosed patients with primary open-angle glaucoma or normal-tension glaucoma were randomly allocated into two equal groups. Group 1 received Brimonidine + Timolol, and Group 2 received Ripasudil + Timolol. Intraocular pressure was assessed at baseline, 1 hour, 1 week, and 4 weeks after advising drug for twice a day.. Safety and tolerability were evaluated during follow-up. Statistical analysis was performed using Student's *t*-test and chi-square test, with $p < 0.05$ considered statistically significant.

Results: Baseline demographic characteristics, clinical profile, and ocular parameters were comparable between the two groups ($p > 0.05$). Both fixed-drug combinations produced a significant reduction in intraocular pressure following initiation of therapy. Intraocular pressure reduction at 1 hour and 1 week was comparable between the two groups ($p > 0.05$). At 4 weeks, Group 2 demonstrated a significantly greater reduction in intraocular pressure compared to Group 1 ($p < 0.001$). Both treatment regimens were well tolerated, with mild and self-limiting adverse effects.

Conclusion: Both Brimonidine + Timolol and Ripasudil + Timolol are effective and safe for short-term management of glaucoma. However, Ripasudil + Timolol demonstrated superior for short-term intraocular pressure control.

Keywords: *Brimonidine, Fixed-drug combination, Glaucoma, Intraocular pressure, Ripasudil, Timolol.*

INTRODUCTION

Glaucoma is a progressive optic neuropathy characterized by structural damage to the optic nerve and corresponding functional visual field loss, which in most cases can be slowed or controlled by adequate reduction of intraocular pressure (IOP).[1] It is the second leading cause of irreversible blindness worldwide, affecting nearly 80 million individuals, with projections estimating an increase to approximately 111.8 million by 2040.[2-4] Asia bears the largest share of this burden, accounting for nearly 60% of global glaucoma cases.[5]In India, the prevalence of glaucoma among adults aged ≥40 years ranges from 2.7% to 4.3%[6], with Primary open-angle glaucoma (POAG) affects approximately 6.48 million individuals. India contributes significantly to global glaucoma-related blindness, accounting for 12.9% of POAG.[7,8]

Elevated IOP remains the most important and consistently identified risk factor in its pathogenesis.[9] Robust cliical evidence demonstrates that lowering IOP significantly reduces the risk of visual field deterioration in patients with POAG.

Although vision loss due to glaucoma is irreversible, disease progression can be effectively controlled through pharmacological therapy, laser procedures, or surgery, with topical medications forming the first-line treatment in most cases.[10]

Several classes of IOP-lowering agents are available, including prostaglandin analogues, β-adrenergic blockers, α_2-adrenergic agonists, carbonic anhydrase inhibitors, and Rho-kinase inhibitors.[11] These agents act by reducing aqueous humor production or enhancing aqueous outflow and are frequently used in combination to achieve sustained 24-hour IOP control. Pharmacological management typically begins with monotherapy; however, a substantial proportion of patients eventually require combination therapy to attain target IOP levels.[12-14]

Timolol, a non-selective β-blocker, reduces aqueous humor production and has long been established as an effective agent in POAG and ocular hypertension.[15] Fixed-dose combinations incorporating Timolol offer advantages such as improved compliance, reduced preservative exposure, and enhanced IOP reduction.[16] Ripasudil, the first ophthalmic Rho-associated protein kinase (ROCK) inhibitor, lowers IOP by increasing trabecular meshwork outflow through cytoskeletal modulation and increased Schlemm's canal permeability.[17-19] Brimonidine, a selective α_2-adrenergic agonist, lowers IOP by reducing aqueous humor production and increasing uveoscleral outflow, achieving further IOP reduction when combined with Timolol.[20]

Despite the advantages of fixed-drug combinations, comparative evidence between the established Brimonidine–Timolol combination and the newer Ripasudil–Timolol combination remains limited, particularly in the Indian population. This study compares the efficacy, safety, and tolerability of the fixed-drug combinations of Brimonidine + Timolol and Ripasudil + Timolol in patients with POAG or NTG.

MATERIALS AND METHODS

This Prospective, Randomized, Hospital-based Interventional study was conducted in the Department of Ophthalmology, Muzaffarnagar Medical College, Muzaffarnagar, Uttar Pradesh. The study population comprised patients attending the ophthalmology outpatient department who were newly diagnosed with POAG or NTG.

A total of 90 patients were enrolled and randomly allocated into two equal groups of 45 patients each using a computer-generated random number table. Eligible participants were assigned unique identification numbers, and allocation to treatment groups was performed to ensure equal probability and minimize selection bias. Group 1 received a fixed-drug combination of Brimonidine + Timolol, while Group 2 received a fixed-drug combination of Ripasudil + Timolol. Patients were enrolled consecutively until the required sample size was achieved.

Inclusion criteria consisted of patients aged more than 20 years, of either sex, newly diagnosed with POAG or NTG. The eye having greater glaucomatous damage with higher IOP was selected as study eye. Patients with a history of ocular trauma, steroid use, previous glaucoma surgery, keratorefractive surgery, optic neuropathy other than glaucoma, known allergy to study drugs, one-eyed, bronchial asthma, chronic obstructive pulmonary disease, cardiovascular disease were excluded from the study.

At baseline, all enrolled patients underwent a comprehensive ophthalmic evaluation, including best-corrected visual acuity assessment(BCVA) using Snellen's chart, slit-lamp examination(SLE) of the anterior segment, (IOP) measurement using Goldmann applanation tonometry, gonioscopy with a Goldmann three-mirror lens, and fundus examination using slit-lamp biomicroscopy with a +90D lens and indirect ophthalmoscopy. Visual field assessment was performed using the Humphrey Visual Field Analyzer (HVF)(24-2 program), and retinal nerve fiber layer (RNFL) thickness was measured using optical coherence tomography(OCT).

Following baseline evaluation, the assigned fixed-drug combination was administered, and IOP was measured again one hour after instillation. Patients were followed up after advising administration of drug twice a day at one week and four weeks. At each follow-up visit BCVA, IOP, SLE, fundus evaluation, assessment of adverse events, and compliance (via verbal questioning) was recorded. All clinical assessments were performed by an independent observer who was not involved in treatment allocation or drug administration.

Statistical Analysis

Data was entered into Microsoft Excel and analyzed using appropriate statistical methods. Continuous variables were expressed as mean and standard deviation and compared using Student's t-test. Categorical variables were expressed as proportions and analyzed using the chi-square test. A 95% confidence interval was used, and a p-value <0.05 was considered statistically significant.

RESULTS

[Table -1] In this study, the age distribution of participants was comparable between Group 1 and Group 2, with the majority of patients belonging to the 41–70-year age range, and no statistically significant difference (p=0.959). The mean age in Group 1 was 55.53±13.24 years, while Group 2 had a mean age of 55.07±13.26 years, with no significant difference (p=0.914). Gender distribution was similar across both groups, with a female predominance in each group (p=0.826). The distribution of glaucoma type was identical, with primary open-angle glaucoma comprising 82.2% and normal-tension glaucoma 17.8% of cases in both groups (p=0.783). The laterality of the affected eye was also comparable between the groups (p=0.671).

Table 1- Baseline Demographic and Clinical Characteristics of Study Participants

Variable	Group 1 (n=45)	Group 2 (n=45)	p value
Age group (years)			
21–30	2 (4.4)	2 (4.4)	0.959
31–40	3 (6.7)	1 (2.2)	
41–50	11 (24.4)	14 (31.1)	
51–60	9 (20.0)	12 (26.7)	
61–70	14 (31.1)	10 (22.2)	
71–80	6 (13.3)	6 (13.3)	
Diagnosis			
NTG	8 (17.8)	8 (17.8)	0.783
POAG	37 (82.2)	37 (82.2)	

[Table-2] Baseline ocular parameters, including cup–disc ratio, Humphrey visual field mean deviation, and pattern standard deviation, were comparable between Group 1 and Group 2, with no statistically significant differences (p>0.05). The glaucoma hemifield test showed that most eyes in both groups were outside normal limits, with no significant difference (p=1.000).

Table 2- Baseline Ocular Parameters and Visual Field Characteristics

Baseline parameter	Group 1 (n=45)	Group 2 (n=45)	p value
Cup–disc ratio (CDR)	0.68 ± 0.08	0.68 ± 0.07	0.967
Humphrey Visual Field (HVF)			
Mean deviation (MD), dB	−5.00 ± 1.88	−4.92 ± 1.72	0.853
Pattern SD (PSD), dB	3.23 ± 0.87	3.34 ± 0.90	0.547
GHT category			
Borderline (BL)	4 (8.9)	3 (6.7)	1.000
Outside normal limits (ONL)	41 (91.1)	42 (93.3)	

[Table-3] Baseline IOP and post-treatment IOP at 1 hour and 1 week were comparable between the two groups (p>0.05). At the 4-week follow-up, IOP was significantly lower in Group 2 compared to Group 1 (p<0.001).

Table 3- Comparison of Intraocular Pressure (IOP) Over Time

Time point	Group 1 (n=45)	Group 2 (n=45)	p value
Baseline	22.31 ± 3.33	23.27 ± 3.05	0.159
1 hour	19.11 ± 3.26	18.78 ± 2.96	0.613
1 week	17.64 ± 3.17	16.73 ± 2.86	0.156
4 weeks	16.67 ± 3.59	14.00 ± 2.95	<0.001

[Table-4] In this study, mild ocular and systemic side effects were observed in both groups, with conjunctival hyperaemia, eyelid erythema, and mild dryness occurring only in Group 2, while itching, mild redness, and mild sedation were noted only in Group 1, and distribution of side effects between the two groups was not statistically significant ($p > 0.05$).

Table 4- Distribution of Side Effects

Side effects	Group 1 (n=45)	Group 2 (n=45)	p value
Conjunctival hyperaemia	0 (0.0)	5 (11.1)	0.066
Eyelid erythema	0 (0.0)	2 (4.4)	0.475
Itching	4 (8.9)	0 (0.0)	0.125
Mild dryness	0 (0.0)	3 (6.7)	0.240
Mild redness	5 (11.1)	0 (0.0)	0.066
Mild sedation	3 (6.7)	0 (0.0)	0.240

DISCUSSION

In the present study, baseline demographic and clinical characteristics were comparable between the two treatment groups, ensuring that any observed differences in outcomes could be attributed to treatment effects rather than confounding factors. Both groups showed similar age distribution, with most patients belonging to the middle-aged and elderly population, which is consistent with the epidemiology of glaucoma. Comparable age profiles have been reported in studies evaluating fixed-drug combinations by Joshi et al[21], Abd Elshafik et al[22], Davawala et al[23], and Tanihara et al[24], supporting the external validity of the present findings.

Gender distribution was comparable between the two groups, with a higher female predominance observed; however, the difference was not statistically significant ($p>0.05$). A similar female predominance has been reported by Davawala et al[23] and Abd Elshafik et al[22],

Both treatment groups had identical proportions of POAG and NTG patients, with POAG constituting the majority. This diagnostic distribution is comparable to previously published studies, where NTG patients were included in smaller proportions, as reported by Joshi et al[21], Toy et al[25], and Davawala et al[23].

Baseline CDR and Baseline visual field parameters (MD and PSD) were comparable between the 2 groups, indicating similar structural disease severity and minimizing the influence of optic nerve asymmetry on IOP reduction. Similar findings have been reported by Yokoyama et al[26] and Davawala et al[23] respectively.

Regarding IOP reduction, both treatment groups showed comparable baseline IOP and similar early reductions at 1 hour and 1 week which can be attributed to the rapid aqueous humor suppressive effect of Timolol present in both combinations. However, at the four-week follow-up, the Ripasudil + Timolol group demonstrated a significantly greater reduction in IOP compared to the Brimonidine + Timolol group. These findings are consistent with published literature. Toy et al[25] observed meaningful IOP reduction when ripasudil was added to existing therapy, comparable to prostaglandin–timolol combinations. Onoe et al[27] also reported sustained IOP lowering after switching to ripasudil-based fixed combinations.

Both treatment regimens were well tolerated, with only mild and self-limiting adverse effects. Brimonidine-related side effects such as mild redness, itching, and sedation, and ripasudil-associated conjunctival hyperemia were consistent with known pharmacological profiles. Similar safety findings have been reported by Joshi et al[21], Divya Tara et al[28], Davawala et al[23], Tanihara et al[24], and Onoe et al[27]. The absence of serious adverse events supports the short-term safety of both fixed-drug combinations.

This randomized controlled interventional study ensured good internal validity through clearly defined eligibility criteria, computer-generated allocation, and objective outcome measures. However, its single-centre design, modest sample size, and short follow-up may limit generalizability and the detection of rare adverse events. Larger, multicentric studies with longer follow-up are recommended to assess long-term efficacy, disease progression, and safety.

CONCLUSION

In our study both treatment groups were comparable at baseline in terms of demographic characteristics, disease profile, and ocular parameters, allowing a balanced comparison. Initiation of therapy with either fixed-drug combination resulted in a reduction in intraocular pressure, demonstrating effective short-term pressure control with both regimens. At the end of the follow-up period, patients receiving the Ripasudil with Timolol combination achieved a greater reduction in intraocular pressure compared to those treated with Brimonidine with Timolol. We concluded that while both Brimonidine with Timolol and Ripasudil with Timolol are effective and safe options for the medical management of glaucoma, the Ripasudil with Timolol combination may offer superior short-term intraocular pressure control.

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