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Comparative Study of Additive IOP Lowering Effects and Safety Profile of Ripasudil 0.4% Combined with Timolol 0.5% and Ripasudil 0.4% Combined with Bimatoprost 0.03% In Primary Open Angle Glaucoma in Indian Eyes

Nidhi Singh[1], Jimmy Mittal[2], Abhishek Singh[3], Niharika[4], Alok Ranjan[5], Alok Kumar Singh[6]

[1]Senior Resident, Department of Ophthalmology, Prasad Institute of Medical Sciences, Lucknow (UP), India
Corresponding Author Email: *nidhi.write[at]gmail.com*

[2]Senior Consultant, Department of Ophthalmology, Vivekananda Polyclinic and Institute of Medical Sciences, Lucknow (UP), India
Email: *drjimmymittal[at]hotmail.com*

[3]Consultant Ophthalmologist, Guru Gorakhnath Hospital, Gorakhpur (UP), India
Email: *shashipremabhi[at]gmail.com*

[4]Consultant Ophthalmologist, Nav Jyoti Netra Kendra, Gorakhpur (UP), India
Email: *niharika10feb[at]gmail.com*

[5]Private practitioner in Patna, Bihar, India
Email: *maildralok[at]gmail.com*

[6]Senior Consultant, Department of Ophthalmology, Vivekananda Polyclinic and Institute of Medical Sciences, Lucknow (UP), India

Abstract: ***Introduction*: IOP lowering is the mainstay of glaucoma treatment. Beta-adrenergic drugs and prostaglandins are some of the commonly used topical medications for this purpose. Ripasudil hydrochloride hydrate, a new Rho-associated coiled-coil-containing protein kinase (ROCK) inhibitor has also emerged as an effective alternative, however, its efficacy as adjuvant to currently used topical medications has not been studied. Aim: To study additive IOP lowering effects and safety profile of the rho-kinase inhibitor (Ripasudil) combined with Timolol or Bimatoprost in Primary Open Angle Glaucoma (POAG). *Materials and Methods*: A total of 80 POAG patients were allocated to four study groups – TM (n=20) receiving topical 0.5% Timolol, TMR (n=20) 0.5% Timolol + 0.4% Ripusadil, BP (n=20) receiving topical 0.03% Bimatoprost and BPR (n=20) – 0.03% Bimatoprost + 0.4% Ripusadil. Change in IOP from baseline was measured at 4, 6 and 8 week follow-ups. *Result*: At last follow-up, mean decline in IOP as compared to baseline was 6.21±1.56, 8.44±1.55, 6.08±1.54 and 8.74±1.53 mmHg respectively in TM, TMR, BP and BPR groups respectively (p<0.001). No major adverse effect was seen in any study group. *Conclusion*: Addition of Ripusadil to conventionally used topical hypotensive agents added to their IOP lowering efficacy without additional burden of adverse effects.***

Keywords: Ripusadil, Primary open angle glaucoma (POAG), Prostaglandin, Beta-adrenergic

1. Introduction

Reduction of intraocular pressure remains to be the mainstay of glaucoma treatment. For this purpose, use of topical hypotensive formulations from different pharmacological groups, viz. topical β-adrenergic antagonists (e.g. timolol, betaxolol), carbonic anhydrase inhibitors (e.g. dorzolamide, brinzolamide), cholinergics (e.g. pilocarpine), α-adrenergic agonists (e.g. brimonidine), prostaglandins (e.g. latanoprost, travoprost), and prostamides (bimatoprost) are widely used (Noecker, 2006; Law, 2007)[1,2]. Ripasudil hydrochloride hydrate, commonly called as Ripasudil is a new Rho-associated coiled-coil-containing protein kinase (ROCK) inhibitor that has shown to be highly effective when used topically for maintenance of IOP. Its mechanism of action is based on acceleration of aqueous humor drainage through the trabecular meshwork and Schlemm's canal which in turn results in drop in IOP (Honjo and Tanihara, 2018)[3]. It has shown to be effective in different glaucoma types even as monotherapy or in combination with others (Kushahara and Nakamura, 2020)[4]. Moreover, its use as an additive to other anti-glaucoma medications targeted to reduce IOP has been shown to be very beneficial (Tanihara *et al.*, 2015; Inazaki *et al.*, 2017; Inoue *et al.*, 2018)[6-7]. Encouraged by these preliminary reports, the present study was planned to compare the effect addition of Ripasudil (0.4%) with Timolol (0.5%) or Bimatoprost (0.03%) for lowering IOP in POAG patients.

2. Material and Method

Study Design: Comparative Study

Study Place: Department of Ophthalmology, Vivekananda Polyclinic and Institute of Medical Sciences, Lucknow.

Study Population: Adult POAG patients (>20 years of age) of both the genders whose IOP was ≥21mm Hg at the time of enrolment.

Sample size: 80 – randomly allocated to four groups of 20 patients each.

Year of Study: September 2020 to August 2021.

Inclusion Criteria: Following was the inclusion criteria for study:

- Male or female with POAG, age of 20 years or older,
- IOP after run-in periods (treated with timolol, 0.5%, twice daily or Bimatoprost, 0.03%, once daily for ≥4 weeks) of 21 mm Hg or higher,
- IOP difference within 3 mm Hg in at least 1 eye at 2 eligibility visits (9 AM) 2 to 14 days apart and treated IOP of less than 35 mm Hg in both eyes.

Exclusion Criteria:

- H/o any ophthalmic surgery
- Presence of secondary, steroid-related, or traumatic glaucoma, and
- BCVA worse than 20/70 in either eye or with severe visual field defects.
- Patients on any other IOP lowering agents, receiving any ophthalmic agents (excluding artificial tears) or corticosteroids, wearing contact lenses, and changing dosages of any concomitant systemic medications that may affect IOP.

Study Groups

TM (n=20) - Timolol 0.5% in combination with placebo.
TMR (n=20) - Timolol 0.5% in combination with 0.4% Ripasudil
BP (n=20) - Bimatoprost 0.03% in combination with placebo
BPR (n=20) - Bimatoprost 0.03% in combination with 0.4% Ripasudil
Intervention period: 8 weeks
Follow-ups: 4, 6 and 8 weeks.

3. Methodology

Demographic details were obtained and ocular examination was performed. At enrolment, measurement of intraocular pressure was done between 11 and 12 a.m. All the patients were asked to use the allocated treatment regimen once a day in morning, topical application of one drop of the parent drug *i.e.* Timolol/ Bimatoprost followed by topical application of one drop of the combination *i.e.* Ripusadil/ Placebo 5-10 minutes after the application of first drug. The patients were advised to keep their eyes close for 5-10 minutes after each application of drug. They were asked to repeat the procedure daily till the period of study at a fixed time preferably between 8 a.m. to 9 a.m. in the morning.

Follow-up examinations were performed at 4, 6 and 8 week intervals. At each follow-up IOP was measured between 11 and 12 a.m. Change in IOP as compared to baseline was assessed.

Statistical Analysis: Data was analyzed using SPSS 21.0 software. Chi-square test, ANOVA and Tukey HSD tests were used for comparison.

4. Results

The study groups were matched for age, sex, socioeconomic status and ocular examination findings (Table 1).

Table 1: Comparison of Demographic profile of patients in different study subgroups

SN	Variable	TM (n=20)	TMR (n=20)	BP (n=20)	BPR (n=20)	'p' value
1.	Mean Age±SD (Range) in years	54.80±13.12 (28-70)	47.50±13.16 (29-69)	53.85±13.03 (30-68)	49.50±13.23 (29-70)	0.248
2.	M:F	10 (50%): 10 (50%)	9 (45%): 11 (55%)	13 (65%): 7 (35%)	10 (50%): 10 (50%)	0.614
3.	SES					
	Upper lower	8 (40.0%)	4 (20.0%)	6 (30.0%)	6 (30.0%)	0.717
	Lower Middle	6 (30.0%)	6 (30.0%)	7 (35.0%)	4 (20.0%)	
	Upper Middle	6 (30.0%)	10 (50.0%)	7 (35.0%)	10 (50.0%)	
4.	Gonioscopy (Shafer Grade)					
	3	8 (40.0%)	12 (60.0%)	11 (55.0%	14 (70.0%)	0.283
	4	12 (60.0%)	8 (40.0%)	9 (45.0%)	6 (30.0%)	
5.	Mean CDR±SD	0.66±0.08	0.64±0.09	0.66±0.07	0.69±0.08	0.431
6.	Mean MD±SD	-4.76±3.78	-8.11±6.04	-8.84±6.17	-7.42±4.14	0.075
7.	Glaucoma Grade (HPA)					
	1	14 (70.0%)	12 (60.0%)	6 (30.0%)	9 (45.0%)	0.078
	2	5 (25.0%)	2 (10.0%)	8 (40.0%)	7 (35.0%)	
	3	1 (5.0%)	6 (30.0%)	6 (30.0%)	4 (20.0%)	

At baseline mean IOP values in groups TM, TMR, BP and BPR were 22.50±2.40, 22.73±2.73, 22.66±2.87 and 22.91±2.58 mmHg respectively, showing no statistically significant difference among the groups (p=0.969). At all the subsequent follow-up intervals mean IOP showed significant decline (p<0.05). At week 8, mean IOP values in groups TM, TMR, BP and BPR were 16.29±2.88, 14.29±2.51, 16.58±2.99 and 14.11±2.12 mmHg respectively. Staitstically, Groups TM and BP had significantly higher mean IOP as compared to that of TMR and BPR groups (p=0.004). At week 8, mean reduction in IOP was 6.21±1.56, 8.44±1.55, 6.08±1.54 and 8.74±1.53 mmHg respectively in TM, TMR, BP and BPR groups showing the reduction in TMR and BPR groups to be significantly higher as compared to that in TM and BP groups (p<0.001) (Table 2).

Table 2: Intergroup Comparison of Mean IOP at baseline and its change different follow-up (Mean±SD, mmHg)

SN	Time	TM (n=20)	TMR (n=20)	BP (n=20)	BPR (n=20)	'p' value
Mean IOP at different follow-up intervals						
1.	Baseline	22.50±2.40	22.73±2.73	22.66±2.87	22.91±2.58	0.969
2.	4 weeks	18.22±2.66*	18.34±3.07*	18.83±3.05*	17.35±2.52*	0.423
3.	6 weeks	17.15±3.56*	17.09±3.12*	17.67±3.37*	16.81±2.65*	0.859
4.	8 weeks	16.29±2.88*[b,d]	14.29±2.51*[a,c]	16.58±2.99*[b,d]	14.11±2.13*[a,c]	0.004
*Within group significant difference as compared to baseline – Paired 't'-test.						
Mean Change in IOP (as compared to baseline) at different follow-up intervals						
1.	4 weeks	-4.28±1.21[d]	-4.40±1.55[d]	-3.83±1.44[d]	-5.56±1.30[a,b,c]	0.001
2.	6 weeks	-5.35±1.82	-5.64±1.56	-4.99±1.66[d]	-6.09±1.42[c]	0.181
3.	8 weeks	-6.21±1.56[b,d]	-8.44±1.55[a,c]	-6.08±1.54 [b,d]	-8.74±1.53[a,c]	<0.001
Significant difference as compared to [a]Group TM, [b]Group TMR, [c]Group BP, [d]Group BPR – ANOVA; Tukey HSD test.						

Incidence of watering and photophobia was seen in 6 to 9 patients in each group. Redness/hyperemia was the most common adverse effect seen in 4 patients of TM group as compared to 16, 18 and 18 patients in groups TMR, BP and BPR respectively. Group TM had significantly lower incidence of hyperemia as compared to other three groups ($p<0.001$) (Fig. 1).

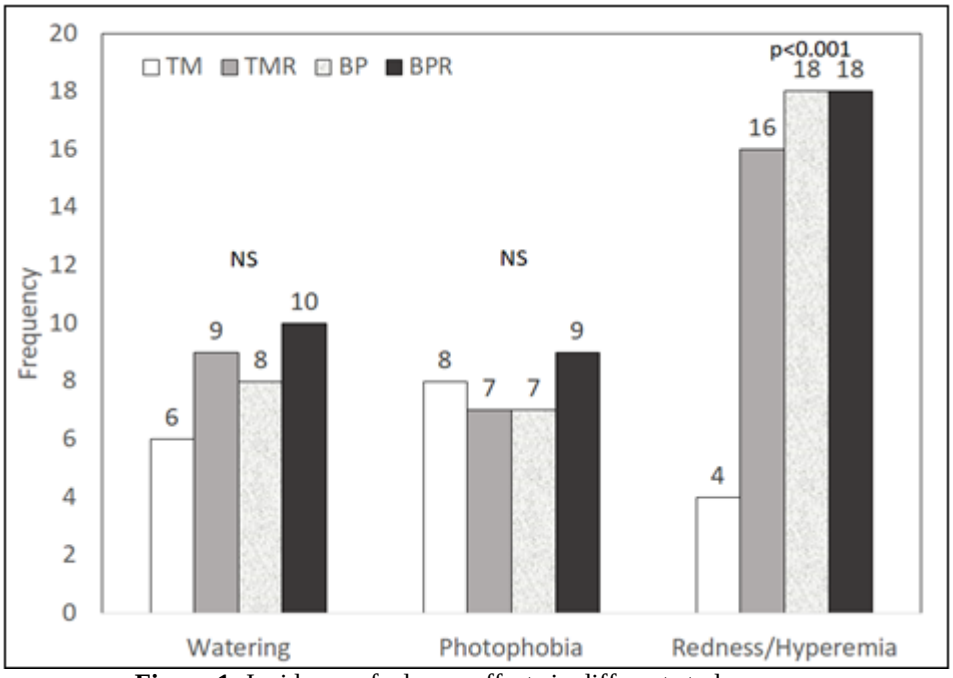

Figure 1: Incidence of adverse effects in different study groups

5. Discussion

The present study showed that addition of Ripusadil to either Timolol or Bimatoprost (two commonly used topical hypotensive agents) helped to enhance their IOP lowering effect even from a short follow-up of four weeks. As far as combinatorial effect of drugs, combination of Ripusadil with either Bimatoprost as well as Timolol produced similar efficacy at the end of follow-up, thus showing that the augmented IOP lowering effect of Ripusadil was similar for both the topical hypotensive agents being evaluated. As such, only minor adverse effects like watering, photophobia and redness/hyperemia were seen for all the four regimens used, however, Timolol showed a relatively better outcome in terms of significantly lower incidence of redness/hyperemia as compared to remaining three regimens. Nevertheless, the two combination groups, *i.e.* TMR and BPR were comparable with respect to additional IOP lowering effect as well as safety profile. Tanihara *et al.*[7] too in their study found addition of Ripusadil to either Timolol or Latanoprost produced similar additional IOP lowering effect even after 4 weeks of intervention. In the present study, we used Bimatoprost instead of Latanoprost and observed similar results. In another study, Tanihara *et al.*[8] observed a significant impact of Ripasudil when used as monotherapy as well as in combination from as early as 8 weeks of assessment. In the present study, we did not use Ripasudil as monotherapy yet found that in combination of either β-adrenergic antagonist or in combination with prostamide Ripasudil had a potential effect in their already existing IOP lowering ability. The additional IOP lowering efficacy of Ripasudil in combination with other hypotensive agents of different classes could be attributed to different mechanisms of their action. Timolol lowers IOP by inhibition of beta receptors on the ciliary epithelium thus inhibiting the aqueous humor production, Bimatoprost through production of glucuronidated metabolites whereas Ripasudil accelerates aqueous humor drainage through the trabecular meshwork and Schlemm's canal to lower IOP (Honjo and Tanihara, 2018)[3]. Despite mild hyperemia being reported as an adverse effect of Ripasudil use[7,8], it is safe to use in combination with increased IOP lowering effect.

6. Conclusion

Additive use of Ripasudil to Timolol or Bimatoprost was safe and helped to increase the IOP lowering efficacy of both the drugs. The efficacy of combination of two drugs with Ripasudil was better than monotherapy.

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