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Research Article

PROSTAGLANDIN ANALOG OR RHO KINASE INHIBITOR – WHICH ONE IS BETTER IN PRIMARY OPEN-ANGLE GLAUCOMA

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ABSTRACT

Objective: The aim of the study was to compare the efficacy, safety, and adverse drug reactions of ripasudil and bimatoprost.

Methods: An open-label, prospective, observational, randomized study was carried out in the Department of Pharmacology M.L.N. Medical College in association with Manohar Das Regional Institute of Ophthalmology, Prayagraj, for 1 year after ethical clearance. A total of 118 patients with primary open-angle glaucoma fulfilling the inclusion and exclusion criteria were taken and randomized into two groups. Only 109 patients completed the study, Group 1 received ripasudil (n=54) and Group 2 received bimatoprost (n=55). Intraocular pressure (IOP), ocular surface disease index (OSDI), tear brake-up time (TBUT), and hyperemia were measured at the initiation of treatment and then measured at different time intervals.

Results: Group 1 and Group 2 patients were observed and followed up for 3 months. At the end of the 2nd, 4th, 6th, and 12th week in Group 1, ripasudil significantly showed better results in reducing IOP as compared to Group 2 bimatoprost. In terms of TBUT, both groups at the 12th week did not show any significant difference. The OSDI score of both groups showed a non-significant difference at the 12th week. At the end of 2nd week, hyperemia was comparable for both groups but ripasudil showed more hyperemia at the end of the 12th week.

Conclusion: We concluded that ripasudil is more effective than bimatoprost in reducing IOP in patients with primary open-angle glaucoma. In terms of adverse effect profile, both drugs showed similar effects in TUBT and OSDI scores. The safety profile of both drugs is similar but the hyperemia score of ripasudil is more than bimatoprost.

Keywords: Bimatoprost, Ripasudil, Dry eye, Hyperemia, Primary open-angle glaucoma, Adverse effect.

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INTRODUCTION

Glaucoma is a chronic, progressive, and degenerative disorder of the optic nerve that produces characteristic vision loss and blindness by damaging the optic nerve [1]. It is often associated with increased intraocular pressure (IOP) (normal range 11 mmHg–21 mmHg) [2]. Glaucoma is also called a – silent thief of sight [3]. There are two types of glaucoma – primary open-angle glaucoma (POAG) and primary closed-angle glaucoma (PACG). Glaucoma is the second cause of blindness and most importantly: It is irreversible [4]. There is no cure for it, but early treatment can often stop the damage and protect vision [5].

The WHO has estimated that 4.5 million people are blind due to glaucoma. In India, glaucoma is the leading cause of irreversible blindness with at least 12 million people affected and nearly 1.2 million people blind from the disease [6]. This prevalence of glaucoma in India is with varying prevalence among different populations and subgroups having a rate of 2.3–4.7%. In regards to subtype, the Indian population has an equal proportion of POAG and PACG [7].

Glaucoma is a chronic progressive disease that cannot be cured but it can be treated by medical, surgical, and other means. The main aim is to reduce IOP with the help of medicine and protect the optic nerve from further damage. The IOP is reduced by decreasing the production of aqueous humor or increasing its outflow.

Medication in the form of eye drops is the first-line treatment in the management of glaucoma. They act by reducing the intraocular pressure and preventing damage to the optic nerve. These eye drops would not cure glaucoma or reverse vision loss, but they can keep glaucoma from getting worse.

In the past few years, there are some new medical treatments have been included in glaucoma therapy. They are prostaglandin analogous and rho kinase inhibitors. Other medical treatments are less efficacious in comparison to prostaglandin analogs and are presently the initial medication of choice. They increase the uveoscleral outflow. PGAs can reduce IOP by 20–35% [8] which is more effective than another group of drugs. These drugs require only once-a-day dosing. The pressure-lowering effect can last up to 2 days. They have a short half-life which reduces the risk of systemic side effects.

Bimatoprost is a synthetic prostamide analog [9] that reduces IOP by increasing aqueous humor outflow through a dual mechanism of action, improving both pressure-dependent and pressure-independent [10].

Rho kinase inhibitors ripasudil are the latest drug for glaucoma treatment. They reduce IOP by 18–41%. Rho kinase (ROCK) inhibitors represent a promising new class of drugs for the treatment of glaucoma [11]. Rho is a group of small GTP-binding proteins [12] by directly acts on the trabecular meshwork; they increase conventional outflow through the Schlemm's canal.

There are very few studies to compare ripasudil a new drug with bimatoprost to which we planned this study to elaborate on which drug is better in the form of effectiveness and safety.

METHODS

This study was an open-label, prospective, observational, and randomized study, designed to demonstrate equivalence between bimatoprost and ripasudil. The study was carried out in the Department of Pharmacology, M.L.N. Medical College in association with the Glaucoma clinic at Regional Institute of Ophthalmology (M.D. Eye Hospital), Prayagraj, for 12 months from March 2021 to April 2022. We included the 118 patients after getting informed consent and based on the inclusion criteria of the present study. The study was conducted after obtaining permission from the Institutional Ethics Committee of M.L.N. Medical College, Prayagraj.

Inclusion criteria

The following criteria were included in the study:

- Patients of either sex aged ≥18 years with a diagnosed case of primary open-angle glaucoma
- Must be able to understand and follow study-related advice.
- Patients who had given written informed consent.

Exclusion criteria

The following criteria were excluded from the study:

- Not willing to get enrolled or consent
- Pregnancy
- Single functioning eye
- Severe central visual field loss
- Intraocular surgery
- Chronic, recurrent, or severe inflammatory eye disease
- Patients will also be excluded if they are unable to discontinue all IOP-lowering ocular medications before the study
- Ocular trauma within the previous 6 months
- Ocular infection or inflammation or ocular laser surgery within the previous 3 months
- Cup to disc ratio >0.8.

The study consisted of six visits conducted during two sequential phases (i) the patient is screened for the POAG/eligibility phase, which included a screening visit, and (ii) the treatment phase, which included the next five visits conducted on the day 1, week 2, week 4, week 6, and week 12. At screening, patients were stopped all pre-study medications, and the new medicine was started after a pre-determined washout period according to the patient's pre-study medication. The enrolment patients were assigned 118 screening numbers 001–118 in the appropriate number sequence and nine patients were left out. The list of patient numbers was randomly generated. At the end of the eligibility visit, eligible patients were randomized in a 1:1 ratio by assigned number and the criteria as described above.

Patients were instructed to instill 1 drop of each assigned drug in both eyes. Bimatoprost was once daily in the evening at the same time [13] (±30 min) for 3 months and the other drug ripasudil was administered used 2 times a day [14] (8:30 am and 8:30 pm) unless a safety issue prevented instillation. Individual patient treatments were masked until all study data were verified, validated, and locked. Safety and efficacy variables were assessed at week 2, week 4, week 6, and week 12 study visits. One eye from each patient was chosen as the study eye, and only the study eye was used in the efficacy analysis. If only one eye of a patient was treated, that eye was selected as the study eye. If both eyes were treated, the worse evaluable eye was selected as the study eye.

Statistical analysis

Data were summarized as mean±standard error (SE) (SE of mean). Both groups were compared by analysis of variance. All statistical analysis was performed using Statistical Package for the Social Sciences software version 21.

RESULTS

A total number of 118 patients who fulfilled the eligibility criteria based on respective inclusion and exclusion criteria and gave written informed consent were included in the study. They were randomly assigned into two groups. Group 1 (n=54) was treated with eye drop ripasudil (0.4%) and group 2 (n=55) was treated with eye drop bimatoprost (0.01%). Out of 118 patients, 109 (92.4%) completed the study. In Group 1, drop out patients were five and in Group 2, drop out patients were four due to which in Group 1 total of 54 patients and in group 2 total of 55 patients were completed the study.

At the time of recruitment along with demographic details following baseline parameters were noted:

1. IOP
2. Tear break-up time (TBUT)
3. Ocular surface disease index (OSDI)
4. Hyperemia.

After the instillation of eye drops in each group of patients according to the treatment assigned, the following parameters were noted at successive follow-up of 12 weeks

1. IOP – observed at the 2nd, 4th, 6th, and 12th week since recruitment
2. TBUT – observed at the 12th week since recruitment
3. OSDI – observed at the 12th week since recruitment
4. Hyperemia – observed at the 2nd and 12th week since recruitment.

Demographic characteristics of patient's

Group 1 included 30 (55.5%) males and 24 (44.4%) females whereas Group 2 included 27 (49.09%) males and 28 (50.9%) females, patients (Table 1 and Fig. 1). The mean ages of the patients in Group 1 were 43.18±11.67 years and in Group 2 were 45.6±12.37 years.

While comparing the parameters IOP, TBUT, OSDI, and hyperemia at baseline in both groups, there were no significant differences (p>0.05) were observed (Table 2). The number of patients having IOP <25 mmHg in Group 1 was 24 (44.44%) and Group 2 was 20 (36%) whereas patients having IOP between 25 and 30 mmHg was 31 (57.40%) in Group 1 and Group 2 was 35 (63.63%).

Effect on IOP

At the end of the 2nd, 4th, 6th, and 12th week in Group 1, ripasudil significantly showed better results in reducing IOP as compared to Group 2 bimatoprost (Table 3 and Fig. 2).

Table 1: Both group male and female ratio

Both group	Males	Females
group 1	30	24
group 2	27	28

Table 2: ANOVA comparison of parameters between Group 1 and Group 2 at baseline

Parameters	Sum of squares	Degree of freedom	Mean square	F	P*-value
IOP baseline	1.939	1	1.939	0.446	0.506
TBUT baseline	19.729	1	19.729	3.236	0.075
OSDI baseline	7.159	1	7.159	0.028	0.867
Hyperemia baseline	0.001	1	0.001	0.006	0.938

(p*<0.05 is significant), IOP: Intraocular pressure, TBUT: Tear break-up time, OSDI: Ocular surface disease index, ANOVA: Analysis of variance

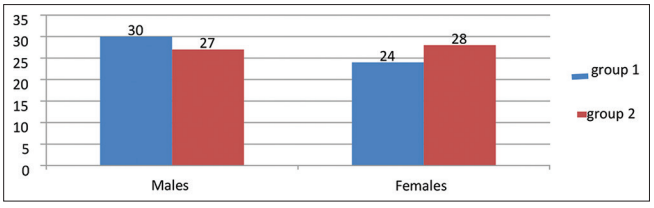

Fig. 1: Both group male and female ratio

Effect on TBUT in both the groups

In terms of TBUT, both groups were comparable and did not show any significant difference (Table 4 and Fig. 3).

Effect on OSDI in both the groups

In terms of OSDI, both groups were comparable and did not show any significant difference (Table 5 and Fig. 4).

Effect on hyperemia in both the groups

At the end of 2nd week, both groups were comparable in terms of hyperemia. However, at the end of the 12th week, Ripasudil was shown more hyperemia in comparison to bimatoprost. Hence, in terms of hyperemia, ripasudil causes more hyperemia than bimatoprost at the end of the 12th week (Table 6 and Fig. 5).

DISCUSSION

This was a prospective, parallel-group, and comparative study between ripasudil (0.4%) eye drop with bimatoprost (0.01%) eye drop to compare the efficacy, safety, and adverse drug reaction (ADR). In this study, we divide the patients into two groups: Group 1 and Group 2. Group 1 was given ripasudil and Group 2 was given bimatoprost.

In the present study, we found that ripasudil eye drops 2 times a day are better than bimatoprost ophthalmic solutions dosed once daily in the evening reducing IOP. IOP in ripasudil group patients was decreased by 8.015 mmHg whereas in the bimatoprost group was decreased by 7.919 from baseline after 3 months of initiation of treatment. We found a significant decrease in mean IOP for all treatment groups from week 2 onward which remained till the end of the study (week 12) while comparing the reduction of IOP in both groups we found a greater decrease in mean IOP for the treatment Group 1 with ripasudil as compared to Group 2 containing bimatoprost treatment groups and the difference was statistically significant.

In our study, we also found that the effect on TBUT of both group ripasudil group as well as bimatoprost group in each follow-up visit was deleterious and the deleterious effects produced by both drugs were not statistically significant when compared between groups.

Table 3: Comparison of means of IOP in Group 1 (RIPASUDIL) and Group 2 (BIMATOPROST) at different time intervals

	t	df	p-value	Mean Difference	Std. Error Difference
IOP BASELINE	-0.668	107	**0.506**	-0.2668	0.3996
IOP WEEK2	-7.235	107	**0**	-3.1239	0.4318
IOP WEEK4	-5.61	107	**0**	-1.7943	0.3199
IOP WEEK6	-4.283	107	**0**	-1.3567	0.3168
IOP WEEK12	-2.609	107	**0.01**	-0.8449	0.3238

Table 4: Comparison of means of TBUT in Group 1 (RIPASUDIL) and Group 2 (BIMATOPROST) at different time intervals

	t	df	p-value	Mean Difference	Std. Error Difference
TBUT BASELINE	1.799	107	**0.075**	0.8509	0.473
TBUT WEEK12	0.923	107	**0.358**	0.4653	0.5042

Table 5: Comparison of means of OSDI in Group 1 (RIPASUDIL) and Group 2 (BIMATOPROST) at different time intervals

	t	df	p-value	Mean Difference	Std. Error Difference
OSDI BASELINE	-0.168	107	**0.867**	-0.5126	3.0518
OSDI WEEK12	-0.535	107	**0.594**	-1.798	3.36

Table 6: Comparison of means of HYPEREMIA in Group 1 (RIPASUDIL) and Group 2 (BIMATOPROST) at different time intervals

	t	df	p-value	Mean Difference	Std. Error Difference
Hyperaemia BASELINE	**0.078**	**107**	**0.938**	**0.0069**	**0.089**
Hyperaemia WEEK2	**-0.55**	**107**	**0.583**	**-0.0628**	**0.1141**
Hyperaemia WEEK12	**2.598**	**107**	**0.011**	**0.2574**	**0.0991**

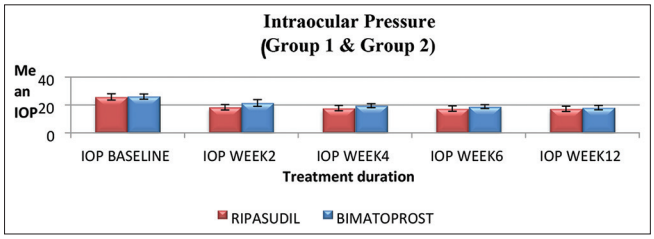

Fig. 2: Comparison of means of IOP in Group 1 (RIPASUDIL) and Group 2 (BIMATOPROST) at different time intervals

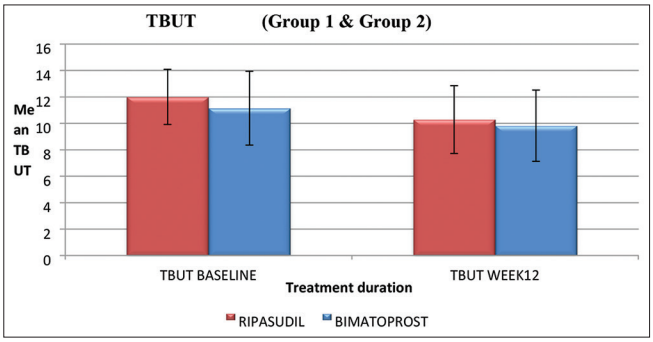

Fig. 3: Comparison of means of TBUT in Group 1 (RIPASUDIL) and Group 2 (BIMATOPROST) at different time intervals

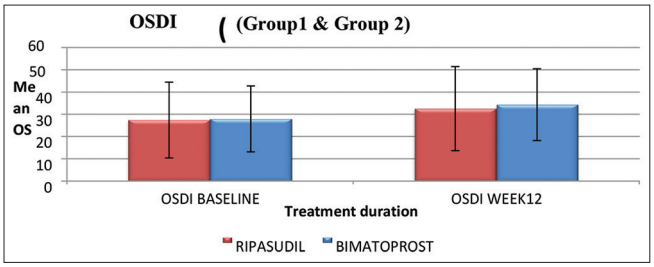

Fig. 4: Comparison of means of OSDI in Group 1 (RIPASUDIL) and Group 2 (BIMATOPROST) at different time intervals

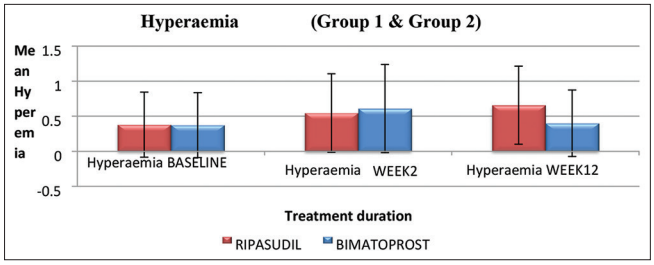

Fig. 5: Comparison of means of HYPEREMIA in group 1 (RIPASUDIL) and group 2 (BIMATOPROST) at different time intervals

We also evaluated OSDI scores and hyperemia scores in our study and found that OSDI scores of ripasudil and bimatoprost increased significantly at the end of the study from baseline scores. OSDI scores have no significant difference in Group 1 as compared to group 2. Hyperemia scores of ripasudil formulations and bimatoprost were found to be increased at 2nd week but at the end of the study (week 12), there was more increase in hyperemia score in the ripasudil group from baseline as compared to bimatoprost group.

Ripasudil is a new drug that was approved in 2014 by food and drug administration (FDA) so there are very few studies were found, and the use of ripasudil is very limited.

A study done by Wanichwecha and Iemsomboon [15] 2005; a multicenter, open-label, and non-comparative study was purposefully designed to reflect the reduction of IOP by 15–20% from baseline IOP by bimatoprost treatment and found that bimatoprost clinically reduces the IOP prescribed as monotherapy. Our study also shows similar results.

Another study done by Tanihara *et al*. [14] 2013 which was a phase II, clinical trial that aimed to identify the optimal dose of K-115 (ripasudil) in 210 patients with POAG or ocular hypertension (OHT). The trial found that 0.4% K-115 (ripasudil) twice daily lowered mean IOP by 3.5 mmHg at trough (before instillation) and by 4.5 mmHg at peak (2 h after instillation) 8 weeks after treatment.

Another study done by Lewis *et al*. [16] 2017 which was a phase I/II, prospective, 24 months, paired eye-controlled clinical trial. At baseline, in open-angle glaucoma patients (n=75), topical bimatoprost 0.03% once daily was administered, and topical bimatoprost in overall IOP reduction through week 16. A single administration controlled IOP in the majority of patients for up to 6 months. Our study also found similar results but the duration of follow-up in our study is 12 weeks.

Another study done by Kusuhara and Nakamura [17] 2020; concerning the efficacy of ripasudil as monotherapy and performed a prospective, randomized, and Latin-square crossover study. They observed a statistically significant reduction in IOP compared with a placebo for at least 7 h after ripasudil instillation in patients with POAG or OHT. In our study, ripasudil also reduces the IOP in treated patients. However, due to ethical issues, we cannot perform the placebo trial.

Ripasudil is well tolerated and effective against almost all subtypes of glaucoma. Regarding safety, conjunctival hyperemia is the most common ADR, but it is unlikely to be a reason for discontinuation as it is usually transient and mild.

CONCLUSION

We concluded that ripasudil is more effective than bimatoprost in reducing IOP in patients of POAG. In terms of adverse effect profile which includes TUBT, OSDI score, and hyperemia score both drugs showed similar effects in TUBT and OSDI score. That is safety profile of both are more or less similar but in hyperemia score, bimatoprost is better than ripasudil.

AUTHORS' CONTRIBUTIONS

Dr. Richa Ojha, Dr. Rakesh Chandra Chaurasiya, Dr. Jagriti Rana, Dr. Dwividendra Kumar Nim, and Dr. Vijay Kumar Singh contributed substantially to the conception, design of the study, analysis, and interpretation of data. All authors discussed the results and commented on the manuscript.

CONFLICTS OF INTEREST

None.

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