Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Clinical and Experimental Ophthalmology

Journal homepage: www.ijceo.org

Original Research Article

A study to evaluate the effect of Ripasudil on the intraocular pressure in open-angle glaucoma

Sugandhi Gauri[1], Gagandeep Kaur[1]*, Neha Sethi[1], Charu Chadha[1], Amit Jain[2], NR Gupta[1], Twinkle Gupta[1]

[1]Dept. of Ophthalmology, Guru Gobind Singh Medical College and Hospital, Faridkot, Punjab, India
[2]Dept. of Pharmacology, Guru Gobind Singh Medical College and Hospital, Faridkot, Punjab

Abstract

Background: Glaucoma is an optic neuropathy characterized by a progressive pattern of damage to the optic nerve and retinal nerve fiber layer (RNFL). The primary treatment modality is the drugs that either promote drainage of aqueous or reduce its production. A new class of drug, Rho-associated coiled-coil containing protein kinase (ROCK) inhibitor has been introduced with a unique mechanism that promotes the conventional uveo-trabecular outflow of aqueous. The purpose of this study is to evaluate the Intraocular Pressure (IOP) lowering effect of Ripasudil and to study its safety profile.
Purpose: To evaluate the effect of Ripasudil in lowering the intraocular pressure in open-angle glaucomas and to study the safety profile of Ripasudil.
Materials and Methods: The study was conducted on 200 eyes of 200 patients. Ripasudil 0.4% twice a day was added to the ongoing treatment and IOP was recorded at follow-up visits.
Results: The mean reduction of IOP from baseline in our study was 1.79 (±0.96) mm Hg at 1 month, 3.36 (±1.35) mm Hg at 3 months, 4.96 (±1.62) mm Hg at 6 months and the mean number of drug used were 1.61 (±0.76). The reduction was statistically significant (p-value <0.001).
Conclusion: The use of Ripasudil is both safe and efficacious as an add-on therapy in open-angle glaucoma patients. The reduction in the primary open-angle glaucoma (POAG), uveitic glaucoma (UG) and steroid- induced glaucoma (SG) groups is similar and larger than those of the pseudoexfoliation glaucoma (PxfG) group. Most common adverse effect is conjunctival hyperemia followed by irritation and blepharitis.

Keywords: Glaucoma, Ripasudil, Rho kinase inhibitors, Anti-glaucoma drugs.

Received: 01-08-2024; **Accepted:** 09-11-2024; **Available Online**: 09-06-2025

1. Introduction

Glaucoma, a chronic optic neuropathy, is a major cause of irreversible blindness around the world.

It was estimated that over 58 million people will have open-angle glaucoma by the year 2020, with 10% being bilaterally blind. Glaucoma is the leading cause of irreversible vision loss and the second leading cause of overall vision loss worldwide. Despite the progressive nature of glaucoma, existing effective treatments can slow or prevent further progression. Early detection and monitoring are critical to the management and preservation of vision and quality of life.[1] IOP reduction is the only reliable, evidence-based management approach to treat glaucoma.[2]

Ripasudil hydrochloride hydrate is the world's first Rho-associated coiled-coil containing protein kinase (ROCK) inhibitor eyedrop that lowers IOP by increasing conventional aqueous outflow through the trabecular meshwork and Schlemm's canal. Rho/ROCK signaling molecules are present in the aqueous outflow pathway and regulate aqueous humor outflow. Cytoskeletal changes are thought to induce retraction and rounding of cells and reduce actin bundles in response to ROCK inhibition by Ripasudil, which may lead to reduced compaction of TM (trabecular meshwork) tissue and increased aqueous outflow.[3] Ripasudil has demonstrated IOP-lowering effects when used as monotherapy or in combination with prostaglandin analogs or beta-blockers.[4] Ripasudil has been shown to protect trabecular meshwork

*Corresponding author: Gagandeep Kaur
Email: drgaganbrar22@yahoo.com

https://doi.org/10.18231/j.ijceo.2025.047

cells from oxidative stress by reducing the expression of IL-6 and IL-8 mRNA after oxidative stress, which suggests it has a protective effect on human trabecular meshwork cells.[5]

Neuroprotection, increased ocular blood flow, anti-inflammation, anti-scarring, decreased macular thickness in eyes with diabetic macular edema and changes in corneal endothelial cells that promote endothelial healing have also been proved as beneficial effects of Ripasudil.[6]

No studies have been done so far comparing the IOP-lowering effects of Ripasudil in different types of open-angle glaucomas in the Indian population.

2. Aims and Objectives

1. To compare the IOP in patients having primary open-angle glaucoma (POAG), uveitic glaucoma (UG), Pseudoexfoliative glaucoma (PxfG) and steroid-induced glaucoma (SG) before and after giving Ripasudil.
2. To study the safety profile of Ripasudil.

3. Materials and Methods

Our study was a hospital-based longitudinal study done over a period of 18 months after getting approval from the institutional ethics committee.

3.1. Sample size calculation

$n = Z^2 P(1-P)/ d^2$
P (Prevalence of glaucoma) = 4.6%[7]
Confidence interval= 95%
Error (d) = 4%
Z= 1.96
1-P= 95.4

n= 109 taking 20% as non-response rate sample size= 132 (minimum) during the course of our study, we were able to enroll more number of patients, so a sample size of 200 eyes of 200 patients were taken. If due to any adverse drug reaction, the drug was stopped, new patients were enrolled in the study to complete the sample size of 200 eyes.

3.2. Sampling technique

A non-probability, consecutive sampling technique was used where all patients who fulfilled the inclusion criteria reporting to the Ophthalmology OPD were taken.

3.3. Inclusion criteria

200 patients of age 20 years or older, who were diagnosed with POAG, UG, PxfG or SG and were on antiglaucoma medications but still had IOP >21mmHg were chosen for the study.

In patients in whom both eyes fulfilled the inclusion criteria, the eye with higher baseline IOP was enrolled in the study.

Eyes were classified into mild, moderate and severe glaucoma categories on the basis of CDR and visual field according to **Table 1** and **Table 2**.[8]

The target IOP was set on a reduction of 30% from the baseline.

3.4. Exclusion criteria

Eyes with narrow angles (Shaffer grade 2 or less)[9] with prior ocular surgery, a history of ocular trauma, hazy media, or any anterior segment abnormality were excluded from the study.

3.5. Ocular examination

After obtaining an informed consent, a detailed medical history and past history was taken. All patients were subjected to a comprehensive ocular examination, which included best corrected visual acuity (BCVA), refraction, anterior segment examination, posterior segment examination, slit lamp bio-microscopy for evaluation of disc, central corneal thickness (CCT), gonioscopy and perimetry.

IOP was measured by Goldmann Applanation Tonometry and corrected readings (compensating for central corneal thickness) were taken as applanation tonometry measurements are affected by central corneal thickness (CCT). For every 10-micron difference in CCT from 520 microns, 0.7mmHg was used as the correction factor.

Eyes were classified into 4 groups- POAG, UG, SG and PxfG and baseline drugs for all patients were recorded. Ripasudil 0.4% was prescribed twice a day along with the ongoing treatment.

3.6. Follow up

Ocular examination for side effects of Ripasudil was done and IOP was recorded at follow-up visits done at 1 week, 1 month, 3 months and 6 months.

3.7. Institutional review board

Ethics committee: Ethical review board, Baba Farid University of Health Sciences (BFUHS), University Centre of Excellence in Research, Academic Block, Sadiq Road, Faridkot, India

Registration number: ECR/854/Inst/PB/2016

This study was performed by following stipulation of Helsinki.

3.8. Statistical analysis

The data was collected and entered into the patient proforma. This data was then analyzed statistically after the desired population was screened using appropriate statistical methodology.

Data were described in terms of range; mean ±standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. To

determine whether the data were normally distributed, a Kolmogorov-Smirnov test was used. Comparison of quantitative variables between the study groups was done using ANOVA with post hoc Tukeys test. For comparing categorical data, Chi-square ($\chi 2$) test was performed and the fisher exact test was used when the expected frequency is less than 5. A probability value (p-value) less than 0.05 was considered statistically significant. All statistical calculations were done using (Statistical Package for the Social Science) SPSS 21version (SPSS Inc., Chicago, statistical IL, USA) statistical program for Microsoft Windows. The following results were obtained.

4. Results

The present study was conducted for the evaluation of the IOP lowering effect and safety of Ripasudil in open-angle glaucoma including POAG, uveitic glaucoma (UG), pseudoexfoliation glaucoma (PxfG) and steroid-induced glaucoma (SG).

Patients aged >20 years of age were enrolled. The following was the scheme (**Figure 1**)

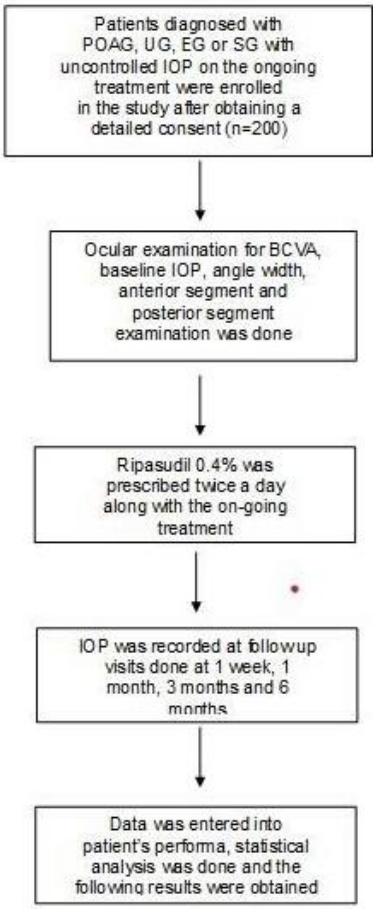

Figure 1: Scheme of enrolling eyes for study

Out of 200 eyes enrolled in the study, 64 (32%) were of Primary Open Angle Glaucoma (POAG), 55 (27.5%) were of Uveitic Glaucoma (UG), 42 (21%) were of Pseudoexfoliation Glaucoma (PxfG) and 39 (19.5%) were of Steroid-induced glaucoma (SG).

Out of 200 patients, 8 patients were < 40 years (4%), 17 patients were between 41-50 years of age (8.5%), 53 patients were between 51-60 years of age (26.5%), 56 patients were between 61-70 years of age (21.9%) and 66 patients were >70 years of age (33%) which are shown in **Figure 2**a as separate for all four groups.

Out of 200 patients, 88 were females (44%) and 112 were males (56%). Overall, 68 patients (34%) had grade 3 angle and 132 (66%) patients had grade 4 angle according to Shaffer's grading on gonioscopy.

99 patients had left eye with higher IOP (enrolled) (49.5%) and 101 patients had right eye with higher IOP (enrolled) (50.5%). Mean drugs used in our study was 1.61 (±0.76).

As shown in **Figure 2**b, the reduction in IOP at the end of 6 months for the POAG group was 4.94 (±1.84) mm Hg, for the UG group was 5.18 (±1.42) mm Hg, for the PxfG was 4.24 (±1.23) mm Hg, and for the SG group was 5.46 (±1.65) mm Hg.

The overall reduction of IOP was statistically significant in all the groups (p-value <0.001) and the reduction of IOP in the POAG group was similar to the reduction in the UG group and the SG group.

At the end of six months, there was a significantly larger reduction in the POAG group [4.94 (±1.84) mm Hg] as compared to the PxfG [4.24 (±1.23) mm Hg].

There was also a significantly larger reduction in the UG group [5.18 (±1.42) mm Hg] as compared to the PxfG [4.24 (±1.23) mm Hg]. The reduction was statistically significant (p value <0.001). The reduction of IOP in the UG group [5.18 (±1.42) mm Hg] was similar to the reduction in SG group [5.46 (±1.65) mm Hg]. There was a significantly larger reduction in the SG group [5.46 (±1.65) mm Hg] as compared to the PxfG [4.24 (±1.23) mm Hg].

The reduction in IOP at the end of 6 months for eyes which were on 1 anti-glaucoma drug was 4.59 (±1.24) mm Hg, the reduction in IOP for eyes which were on 2 anti-glaucoma drugs was 5.23 (±1.49) mm Hg and the reduction in IOP for eyes which were on 3 anti-glaucoma drugs was 5.76 (±2.43) mm Hg as shown in **Table 3**.

The mean reduction in IOP at 1 week was 0.38 (±0.72) mm Hg, at 1 month was 1.79 (±0.96) mm Hg, at 3 months was 3.36 (±1.35) mm Hg and at 6 months was 4.96 (±1.62) mm Hg as shown in **Figure 2**c. This reduction was statistically significant (p-value <0.001).

A total of 27 eyes required additional treatment (13.5%), 12 in the POAG group (18.8%), 9 in the UG group (16.4%), 3 in the PxfG (7.1%) and 3 in the SG group (7.7%).

Figure 2d is a bar graph depicting the adverse drug reactions, most common being conjunctival hyperemia in 53 patients (26.5%), followed by irritation in 19 patients (9.5%), blepharitis in 17 patients (8.5%) and honeycomb edema in 3 patients (1.5%).

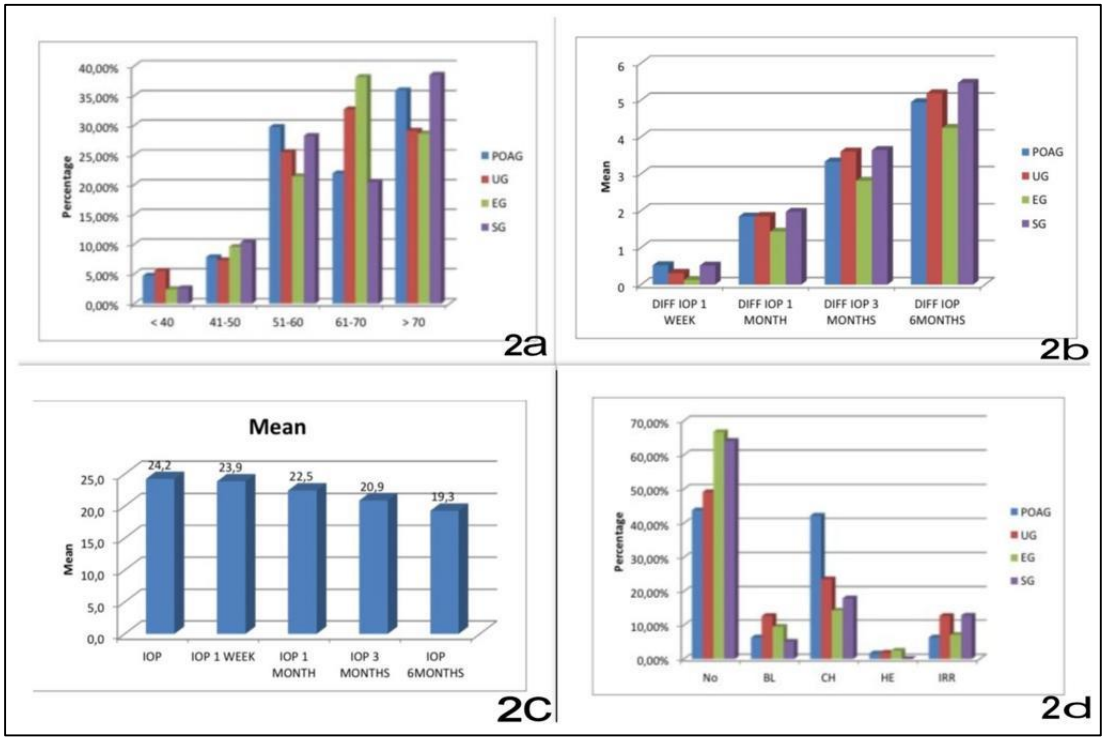

Figure 2: a): Bar graph showing frequency and percentage of distribution cases according to age group; **b)**: Bar graph showing overall reduction of IOP after addition of Ripasudil in primary open angle glaucoma (POAG), uveitic glaucoma (UG), pseudoexfoliation glaucoma (PxfG), and steroid induced glaucoma (SG) group; **c):** Bar graph showing mean reduction of IOP in all groups; **d)**: Bar graph showing distribution of cases according to adverse drug reaction

Table 1: Variation of CDR in different groups

CDR	POAG	UG	PxgG	SG
<0.5	17	32	20	12
0.5-0.8	37	19	19	26
>0.8	10	4	3	1

Table 2: Severity of glaucoma

Early defect	Moderate defect	Severe defect
Mean deviation between 0 and -6 dB, and at least one of the following:	Mean deviation between -6dB and -12 dB, and at least one of the following:	Mean deviation between <-12 dB, and at least one of the following:
A cluster of more than or equal to 3 points on the pattern deviation plot at an expected location of the visual field depressed below the 5% level, at least one of which is depressed below the 1% level, or	More than/equal to 25% but <50% points on the pattern deviation plot depressed below the 5% level, and more than/equal to 15% but < 25% of points depressed below the 1% level, or	More than or equal to 50% but <75% of points on the pattern deviation plot depressed below the 5% level and more than or equal to 25% but<50% of points depressed below the 1% level, or
A glaucomatous hemifield test result outside the normal limits	Only 1 hemifield with a point with sensitivity <15dB within 5 degrees of fixation	Points within the central 5 degrees with a sensitivity <15dB in both hemifields

Table 3: Number of drugs being used by patients in different groups before starting Ripasudil

Drugs	POAG	UG	PxfG	SG
1	24	37	32	20
2	24	8	8	13
3	16	10	2	6

5. Discussion

Ripasudil lowers IOP by increasing the conventional aqueous outflow through the trabecular meshwork and Schlemm's canal, hence effective in open-angle glaucomas. So, gonioscopy was done to exclude angle closure cases from this study.

Our study aimed to compare the IOP in patients having primary open-angle glaucoma (POAG), uveitic glaucoma (UG), exfoliative glaucoma (PxfG) and steroid-induced glaucoma (SG) before and after giving Ripasudil.

In our study, IOP reduction from baseline was 4.94 (±1.84) mm Hg in the POAG group, 5.18 (±1.42) mm Hg for the UG group, 4.24 (±1.23) mm Hg for the PxfG, 5.46 (±1.65) mm Hg for the SG group, at the end of 6 months which were statistically significant. (p-value <0.001). A mean reduction of 4.81 (±1.40) mm Hg was reported by Shino Sato et al. in the POAG group after the addition of Ripasudil, which was similar to our study.[10] Akiko Futakuchi et al reported mean IOP reductions from baseline in the UG, PxfG and SG groups as 7.39 (±11.02) mmHg, 4.25 (±6.55) mmHg, and 9.26 (±11.40) mmHg, respectively.[11]

Our study reported that the reduction in the POAG, UG and SG groups were similar and larger than those of the PxfG. A similar result was obtained by Akiko Futakuchi et al and was thought to be related to the higher baseline IOP levels of the POAG, UG and SG groups as compared to the PxfG.[11]

The reduction in IOP at the end of 6 months for eyes which were on 1 anti-glaucoma drug was 4.59 (±1.24) mm Hg, the reduction in IOP for eyes which were on 2 anti-glaucoma drugs was 5.23 (±1.49) mm Hg and the reduction in IOP for eyes which were on 3 anti-glaucoma drugs was 5.76 (±2.43) mm Hg, which was statistically significant. (p-value <0.001).

The larger reduction can be attributed to the additive IOP lowering effect of ripasudil with prostaglandin analogs as well as beta blockers as reported in the studies done by Hidenobu Tanihara et al and Rei Sakata et al.[12,13]

The most common adverse drug reaction reported in our study was conjunctival hyperemia which was reported by 53 patients (26.5%), followed by irritation reported by 19 patients (9.5%) and followed by blepharitis reported by 17 patients (8.5%).

A similar order of adverse drug reactions were reported by Hidenobu Tanihara et al, Shino Sato et al, Takashi Komizo et al, Akiko Futakuchi et al, and Sentaro Kusuhara et al with conjunctival hyperemia being the most common adverse drug reaction. Conjunctival hyperemia is thought to be related to the dilation of blood vessels associated with the alteration in the properties of vascular endothelial cells.[10-12,14,15]

Three eyes had reticular, honeycomb corneal edema which was noticed when the patients came for follow-up with complaints of blurring of vision.

The drug was discontinued and patients were managed with topical hyperosmotic saline instilled 4 times a day, for 15 days, after which the edema resolved.

A total of 27 (13.5%) patients required additional treatment after 1 month of addition of Ripasudil and no additional treatment was required by 173 patients (86.5%).

5.1. Strengths of our study

Our study was a prospective study, so the patients were closely followed and treated.

All the cases were evaluated and managed by a single clinician, hence proving the consistency of our study.

Prior studies were done on POAG or secondary open angle glaucomas, but our study has compared the results for both primary and secondary open angle glaucomas.

Ripasudil is both safe and effective in all types of open angle glaucomas as an add on therapy. The adverse drug reactions could be attributed to Ripasudil, as a they were not present at the baseline before starting Ripasudil even though combination of drugs was used.

6. Limitations of our Study Include

A relatively small sample size was taken into consideration while the duration of the disease was not taken into account. Patients were followed up for a shorter duration so long-term efficacy and complications could not be studied.

Despite the limitations, our study clearly demonstrates the efficacy and safety of Ripasudil in open angle glaucomas and we conclude that-

1. Ripasudil lowers IOP by increasing the conventional aqueous outflow through the trabecular meshwork and Schlemm's canal, hence effective in open angle glaucomas.
2. The use of Ripasudil is both safe and efficacious as an add on therapy in open-angle glaucoma patients.

3. It has an additive IOP-lowering effect with other class of antiglaucoma drugs.
4. The reduction in the POAG, UG and SG groups is similar and larger than those of the PxfG.
5. Most common adverse effect is conjunctival hyperemia followed by irritation and blepharitis.

Further research is required for studying long term safety and efficacy of ripasudil in Indian population.

7. Source of Funding

None.

8. Conflict of Interest

None.

References

1. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*. 2006;90(3):262–7.
2. Nakai Y, Inoue K, Moriyama R, Wakakura M, Inoue J, Tomita G. Current status of glaucoma therapy at private practices and a private ophthalmology hospital. *Atarashii Ganka (J Eye).* 2008;25(11):1581–5.
3. Koga T, Koga T, Awai M, Tsutsui J, Yue BY, Tanihara H. Rho-associated protein kinase inhibitor, Y-27632, induces alterations in adhesion, contraction and motility in cultured human trabecular meshwork cells. *Exp Eye Res*. 2006;82(3):362–70.
4. Tanihara H, Inoue T, Yamamoto T, Kuwayama Y, Abe H, Suganami H, et al. Additive Intraocular Pressure-Lowering Effects of the Rho Kinase Inhibitor Ripasudil (K-115) Combined With Timolol or Latanoprost: A Report of 2 Randomized Clinical Trials. *J Am Med Assoc Ophthalmol.* 2015;133(7):755–61.
5. Mochizuki H, Murphy CJ, Brandt JD, Kiuchi Y, Russell P. Altered stability of mRNAs associated with glaucoma progression in human trabecular meshwork cells following oxidative stress. *Invest Ophthalmol Vis Sci.* 2012;53(4):1734–41.
6. Minami Y, Song YS, Ishibazawa A, Omae T, Ro-mase T, Ishiko S, et al. Effect of ripasudil on diabetic macular edema. *Sci Rep.* 2019;9(1):3703.
7. Ahmad A, Ahmad SZ, Khalique N, Ashraf M, Alvi Y. Prevalence and Associated Risk Factors of Glaucoma in Aligarh, India–A 83 population based study. *J Delhi Ophthalmol Soc*. 2020;31(1):36–40.
8. Mittal D, Dubey S, Gandhi M, Pegu J, Bhoot M, Gupta YP. Discriminating ability of Cirrus and RTVue optical coherence tomography in different stages of glaucoma. *Indian J Ophthalmol.* 2018;66(5):675–80.
9. Chan RY, Smith JA, Richardson KT. Anterior segment configuration correlated with Shaffer's grading of anterior chamber angle. *Arch Ophthalmol.* 1981;99(1):104–7.
10. Sato S, Hirooka K, Nitta E, Ukegawa K, Tsujikawa A. Additive Intraocular Pressure Lowering Effects of the Rho Kinase Inhibitor, Ripasudil in Glaucoma Patients Not Able to Obtain Adequate Control After Other Maximal Tolerated Medical Therapy. *Adv Ther*. 2016;33(9):1628–34.
11. Futakuchi A, Morimoto T, Ikeda Y, Tanihara H, Inoue T; ROCK-S study group collaborators. Intraocular pressure-lowering effects of ripasudil in uveitic glaucoma, exfoliation glaucoma, and steroid-induced glaucoma patients: ROCK-S, a multicentre historical cohort study. *Sci Rep*. 2020;10(1):10308.
12. Tanihara H, Inoue T, Yamamoto T, Kuwayama Y, Abe H, Suganami H, et al. Intra-ocular pressure-lowering effects of a Rho kinase inhibitor, ripasudil (K-115), over 24 hours in primary open-angle glaucoma and ocular hypertension: a randomized, open-label, crossover study. *Acta Ophthalmol.* 2015;93(4):e254–60.
13. Sakata R, Fujishiro T, Saito H, Honjo M, Shirato S, Aihara M. The Additive Effect of ROCK Inhibitor on Prostaglandin-Treated Japanese Patients with Glaucoma Indicating 15 mmHg and Under: ROCK U-15. *Adv Ther.* 2021;38(7):3760–70.
14. Komizo T, Ono T, Yagi A, Miyata K, Aihara M. Additive intraocular pressure-lowering effects of the Rho kinase inhibitor ripasudil in Japanese patients with various subtypes of glaucoma. *Jpn J Ophthalmol*. 2019;63(1):40–5.
15. Kusuhara S, Nakamura M. Ripasudil Hydrochloride Hydrate in the Treatment of Glaucoma: Safety, Efficacy, and Patient Selection. *Clin Ophthalmol.* 2020;14:1229–36.

Cite this article: Gauri S, Kaur G, Sethi N, Chadha C, Jain A, Gupta NR, Gupta T. A study to evaluate the effect of Ripasudil on the intraocular pressure in open-angle glaucoma. *Indian J Clin Exp Ophthalmol*. 2025;11(2):257–262.