ORIGINAL ARTICLE

Additive Intraocular Pressure Lowering Effects of Ripasudil in Patients with Primary Open Angle Glaucoma and Ocular Hypertension

Asma Jabeen, Ashok K Sharma, Hans Raj Sharma

Abstract

Introduction: Glaucoma is one of the leading cause of irreversible blindness worldwide. Among the affected ones, approximately 50% are not aware of it, because of its asymptomatic nature, especially in the early stages. Ripasudil Hydrochloride Hydrate is a novel drug, being the Rho-associated coiled-coil-containing protein kinase (ROCK) inhibitor eye drop that increases conventional aqueous outflow through the trabecular meshwork and Schlemm's canal and thus lowers the intraocular pressure. **Material and Methods:** This prospective study included the first 150 consecutive eyes in patients of uncontrolled glaucoma with IOP > 21 mmHg despite maximal topical anti-glaucoma medications in at least one eye and aged eighteen or above. The patients with neovascular glaucoma, closed or barely open anterior chamber angle or with history of ocular surgery including refractive surgery were excluded. The purpose and nature of the study were explained in detail, and informed consent was obtained from all patients. **Results:** This study included 115 patients with 150 affected eyes. The mean age of patients in this series was 43.6 years with a range of 24-73 years. Right eye was affected in 47, left in 33 patients and the remaining 35 patients had bilateral involvement. The mean pachymetry was 521.13 μm in right eye and 523.53 μm in left eye and the mean cup disc ratio was 0.8 and 0.7 in right and left eye respectively. The mean baseline intraocular pressure in our series was 18.60 mmHg +- 7.60 mmHg. The mean IOP at six month follow up visit (final follow-up) was 11.83mmHg +- 4.45, which was statistically significant. The mean reductions in IOP at one month was 12.64mmHg, at 3 months follow up 12.07mmHg. **Conclusion:** The results of our study implies that ripasudil is a favourable anti glaucoma drug that can lower intraocular pressure. The additive pressure lowering effects of ripasudil in addition to existing maximal therapy can be because of different mechanism of action, it can delay or evade surgery in glaucoma. Transient conjunctival hyperaemia, not necessitating discontinuation was the most common complication in this series.

Keywords

Ripasudil, ROCK Inhibitors, Glaucoma, Ocular Hypertension

Introduction

Glaucoma is one of the leading causes of irreversible vision loss globally and can be considered as unresolved public health problem.[1] Its global prevalence in the age group 40–80 years old is expected to increase to 111.8 million in 2040 from 76 million in 2020.[2]Among the affected ones approximately 50% are not aware of it because of its asymptomatic nature especially in the early stages. Based on prevalence studies, 90% of glaucoma

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is undetected especially in developing countries, and hence near about one fifth of the patients become blind in either or both the eyes.[3] It is a well-known multifactorial disease but so far intraocular pressure (IOP) has been shown to be one of the significant risk factors for developing glaucoma, thus has been recognized as primary modifiable risk factor. Initial treatment for glaucoma most commonly involves the use ofmedical therapies to lower the IOPto a range that preserves structural and functional testing results.[4] These types of therapeutic interventions include the use of first-line drugs such as prostaglandin analogues and b-blockers. However,in certain patients, it is necessary to add atleast 2 or more medications to achieve their target IOPs as reported by The Ocular Hypertension Treatment Study.[5]

Ripasudil Hydrochloride Hydrate being the Rho-associated coiled-coil-containing protein kinase (ROCK) inhibitor eye drop that increases conventional aqueous outflow through the trabecular meshwork and Schlemm's canal and thus lowers the intraocular pressure. It binds to ROCK1 and ROCK2 downstream effector proteins and activates them. Further it enhances cytoskeletal remodeling and synthesis, which results in increased tissue contraction and stiffness. Various preclinical studies have demonstrated the effect of ROCK inhibitorson cells component responsible for trabecular outflow pathway.[6] Many recent studies demonstrated that it also causes inhibition of immune cell infiltration and inflammatory cytokine production thus adding to its anti-inflammatory effects.[7] In the year 2014, ROCK inhibitor Ripasudil was approved as an intra-ocular pressure lowering drug under the brand name Glanatec (ophthalmic solution 0.4%). On Jan 6, 2020, Ripasudil was first launched in India as a newer molecule for anti-glaucoma therapy. Its mechanism of action varies as compared to other available IOP lowering medications which promote uveoscleral outflow or suppress aqueous humor production. ROCK inhibitors have also shown to reduce IOP even in non- or weak responders as compare to other IOP lowering drugs. Various clinical trials have been done that demonstrates that Ripasudil lowers IOP effectively in patients with Primary open angle glaucoma and ocular hypertension. In the present study the purpose was to evaluate the additive effect of Ripasudil in terms of overall IOP reduction in patients with primary open angle glaucoma and ocular hypertension.[8,9]

Material and Methods

This prospective study was conducted at Upgraded Department of Ophthalmology, Government Medical College, Jammu, following the Declaration of Helsinki. The purpose and nature of the study were explained in detail, and informed consent was obtained from all patients. The first 150 eyes of consecutive patients between December 2020 and January 2022 were prospectively enrolled.Inclusion criteria were as follows:

1. Patients aged 18 years or older and
2. Patients with uncontrolled glaucoma with IOP >21 mmHg despite maximal topical anti-glaucoma medications in at least one eye.

The exclusion criteria were as follows:

1. Patients with neovascular glaucoma
2. Closed or barely open anterior chamber angle
3. History of acute angle-closure or ocular trauma
4. Any history of ocular surgery including refractive surgery, glaucoma filtering surgery, or vitreous surgery
5. Any history of cataract surgery and
6. Inability to adhere to the treatment and follow-up plan.

With the exception of ripasudil, all patients enrolled in the study had been previously receiving the maximal tolerated medical therapy.The eye with higher baseline IOP was selected for analysis. IOP was measured via Goldman applanation tonometry, and was recorded prior to ripasudil treatmentand 1 month ± 1 week, 3 months ± 2 weeks, and 6 months ± 4 weeks after initiating ripasudil treatment (0.4%, twice daily). Dropout for any reason, including additional medication, surgery, or adverse events, was considered as study discontinuation. Comparisons for the clinical characteristics were performed using appropriate statistical methods. $P < 0.05$ was considered statistically significant. All statistical values were presented as the mean ± standard deviation (SD).

Results

This study included115 patients with 150 affected eyes. There were 64 males and the remaining 51 were females. The mean age of patients in this series was 43.6 years with a range of 24-73 years. Right eye was affected in 47, left in 33 patients,and the remaining 35 patients had bilateral involvement. All the patients in our series were already on two or more anti-glaucoma medications before the institution of ripasudil. The mean pachymetry was 521.13 μm in right eye and 523.53 μm in left eye and the mean cup disc ratio was 0.8 and 0.7 in right and left eye respectively. The mean baseline intraocular pressure in our series was 18.60mmHg+- 7.60 mmHg.The mean IOP at subsequent visits was statistically lower compared to baseline intraocular pressure. The mean IOP at six month

follow up visit (final follow-up) was 11.83mmHg +- 4.45, which was statistically significant. The mean reductions in IOP at one month was 12.64mmHg, at 3 months follow up 12.07mmHg (table 1). The mean number of glaucoma medications was also decreased in patients on ripasudil treatment at the final visit.This study described a statistically significant reduction in intraocular pressure at all the follow up visits ($P < 0.00001$) with the highest reduction seen at six months. The most common side effect of ripasudil seen in our patients was mild conjunctival hyperaemia, however, none of the patients developed any side effect necessitating discontinuation of treatment.

Table 1: Demographic and other variables of patients on Ripasudil treatment.

S.No.	Characteristics		Value
1	Age	Mean Range	43.6 (years) 24-73 (years)
2	Gender	Male Female	64 51
3	Laterality	Right eye Left eye Bilateral	47 33 35
4	Intraocular Pressure	Pre-initiation Post-initiation 1 month 3 month 6 month	18.60 +- 7.60 mm Hg 12.64 +- 5.12 mm Hg 12.07 +- 4.71 mm Hg 11.83 +- 4.45 mm Hg
5	Pachymetery	Right eye Left eye	521.13μm 523.53μm
6	Cup Ratio	Right eye Left eye	0.8 0.7

Discussion

This series determined the additive intra-ocular pressure reducing effects of ripasudil instillation alongside other anti-glaucoma medications in varying combinations. Currently, β blockers and CAI are used to suppress aqueous humour production, whereas, PGAs, α_1 and α_2 agonists are used to promote uveoscleral outflow. The selection of these anti glaucoma medications is dependent on target IOP of each individual patient and characteristics of patient and disease. In this study, we noted a significant reduction in IOP in all the patients at all time intervals, the maximum being at 6 months of starting ripasudil in this series. In a similar study by Kawara *et al*., the authors observed that the median IOP was significantly lowered from 19.0 (17.0–22.5) mm Hg at baseline to 16.0 (15.0–20.0) mm Hg at 6 months.[10] In our study, all patients having primary open angle glaucoma showed a reduction in IOP from baseline 18.60 mm Hg to 12.07 mm Hg at 3 months and 11.83mm Hg at final follow up of six months, which was statistically significant ($P < 0.00001$). All patients in our series reached a predefined target IOP at the end of the study (100%). These pressure lowering effects of Ripasudil and other ROCK inhibitor agents might be due to the direct vasodilating action in the posterior chamber of the eye, and such results are validated by other studies as well.[11-14] In an animal model study the authors demonstrated that the drug ripasudil increased retinal blood flow in cats.[15] In another study on safety and efficacy of ripasudil in 27 patients, the authors reported a statistically significant reduction in IOP at all time durations ($P < 0.00001$) with the maximum reduction at 3 months without any major complication.[16] In a study on Japanese population, the authors demonstrated that IOP was significantly reduced compared with that at pre initiation at each time-point ($P < 0.05$). Differences in IOP between the first and second periods of the study were not statistically significant ($P = 0.058$). the common adverse effects observed in their study of 312 patients leading to discontinuation of treatment included blepharitis (15.7%) and conjunctival hyperaemia (9.0%).[17] In another large scale observational study including 3374 patients with glaucoma or ocular hypertension were evaluated for safety and 3178 for effectiveness of ripasudil over a mean 524.5-day observational period. The authors noted that 25.3% of the patients experienced adverse drug reactions; the most common were blepharitis (8.6%), conjunctival hyperaemia (8.5%), and conjunctivitis (6.3%) in order of occurrence. IOP decreased substantially from baseline with ripasudil; they observed meaningful decrease of IOP in primary open-angle glaucoma, normal-tension glaucoma, primary angle-closure glaucoma, and secondary glaucoma, and ocular hypertension.[18] Although the initial results of Ripasudil are encouraging still large scale studies from different regions with variable population and patient characteristics are needed to further establish its role and position in the management of Glaucoma.

Conclusion

The results of our study implies that ripasudil is a favourable anti glaucoma drug that can lower intraocular pressure. The additive pressure lowering effects of ripasudil in addition to existing maximal therapy can be because of different mechanism of action, it can delay or

evade surgery in glaucoma. Transient conjunctival hyperaemia, not necessitating discontinuation was the most common complication in this series. There was significant reduction in IOP that was apparent at 3 months and was maintained till last follow up. This study suggests that ripasudil is a promising agent for the treatment of glaucoma when used in various dosage forms or in combination with other glaucoma therapies. It is well tolerated and effective against almost all subtypes of glaucoma.

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Conflicts of Interest
There are no conflicts of interest.

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