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Safety, efficacy, and patient selection of ripasudil in patients with uncontrolled glaucoma with maximum conventional medical therapy

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Purpose: Ripasudil hydrochloride hydrate (0.4%) is the first Rho-associated protein kinase (ROCK) inhibitor eye drop that lowers intraocular pressure (IOP) by increasing conventional aqueous outflow through the trabecular meshwork and Schlemm's canal. We aimed to evaluate the safety and efficacy of ripasudil in patients using the maximum topical anti-glaucoma medications and with uncontrolled IOP. **Methods:** In our prospective interventional study, we enrolled 27 eligible and consenting patients (46 eyes) who presented to us between January 2021 and June 2021. Ripasudil 0.4% was added as adjunctive therapy to the ongoing glaucoma treatment. On follow-up visits at 7 days, 15 days, 1 month, 2 months, and 3 months, the visual acuity, IOP with applanation tonometer, anterior segment, and fundus were evaluated. The IOP before and after the use of ripasudil eye drops was compared by paired *t*-test. **Results:** Among the 27 patients, 18 were males and 9 were females. A statistically significant reduction in IOP was noted at all time durations ($P < 0.00001$) with the maximum reduction at 3 months with all patients achieving their target IOP. No patient developed any side effects necessitating the omission of ripasudil. The most common adverse event noted was conjunctival hyperemia (22 patients), which was mild and transient. **Conclusion:** Ripasudil showed additional IOP-lowering effect with other antiglaucoma medications and exhibited no significant side effects.

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Glaucoma, a chronic optic neuropathy, is a major cause of irreversible blindness around the world.[1,2] Although the pathogenesis of glaucoma remains unclear, progressive degeneration in the retinal ganglion cells (RGCs) is a key cellular event that leads to characteristic glaucomatous optic disc changes with associated visual field loss.[3] The main effective mechanism for the treatment of glaucoma is lowering the intraocular pressure (IOP). Although treatment modalities for IOP lowering include topical and systemic medical therapy as well as laser and incisional surgical procedures, topical hypotensive therapy is the most commonly used strategy. For patients on medical therapy, clinical trial experience indicates that approximately 40 to 50% of patients require two or more medications to adequately lower the IOP.[2] There are five classes of topical ocular hypertensive medical agents that are commonly used for long-term therapy: beta-adrenergic antagonists, carbonic anhydrase inhibitors (CAI), prostaglandin analogs (PGAs), alpha-2-selective adrenergic agonists, and cholinergics. Many patients are unable to tolerate one or more of these agents either due to allergy, other side effects, or contraindications. Even when all four agents are used in combination, IOP lowering can often be insufficient. Many patients require surgery to achieve a sufficiently low IOP to stabilize their disease process; however, such procedures are not free from the risks of short- and long-term complications. Therefore, there has been a need for additional and more effective medications for IOP lowering.

Ripasudil hydrochloride hydrate is the world's first Rho-associated coiled-coil-containing protein kinase (ROCK) inhibitor eye drop that lowers the IOP by increasing the conventional aqueous outflow through the trabecular meshwork and Schlemm's canal.[4] Rho is a Ras homolog of small GTPase, which regulates various fundamental cell behaviors through Rho/ROCK signaling. In trabecular meshwork cells, Rho guanine nucleotide exchange factor (RhoGEF) activates Rho by catalyzing GDP–GTP exchange following the binding of the agonist to its receptor (e.g., G-protein-coupled receptor). The GTP-bound Rho then binds to the downstream effector proteins ROCK1 and ROCK2, activating them. Activated ROCK1/2 phosphorylates myosin light chain (MLC) and Lin-1/Isl-1/Mec-3 kinase (LIMK) enhances cytoskeletal remodeling and synthesis and assembly of the extracellular matrix, resulting in increased tissue contraction and stiffness.[4-6] By inhibiting Rho-kinase enzyme ripasudil eye drops inhibit cytoskeletal remodeling and extracellular matrix synthesis, which leads to decreased contraction and stiffness that further leads to increased aqueous outflow through the trabecular meshwork

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and Schlemm's canal. In vascular smooth muscles, the Rho/ROCK pathway is expressed, and ROCK inhibitors relax various vascular smooth muscles, which increase the ocular and retinal blood flow by inducing vasodilatation and, hence, providing neuroprotective action. Hence, ROCK inhibitors may improve the blood flow rate in the optic nerve head. The effects of ROCK inhibitors on cell components responsible for the trabecular outflow pathway have been well documented in preclinical studies.[7] In cultured trabecular meshwork cells, the addition of ROCK inhibitors caused morphological changes accompanied by disruption of actin bundles and disassembly of focal adhesion.[7] ROCK inhibitors also affect cultured Schlemm's canal endothelial (SCE) cells and increase their permeability.[8,9] Many animal experiments support the efficacy of ROCK inhibitors in IOP reduction,[10] and several *ex vivo* and *in vivo* experiments demonstrated conventional outflow tissue responses to ROCK inhibitors: increased aqueous humor outflow,[8] expanded outflow route,[9] and suppression of the fibrogenic response.[10] Ripasudil has a plasma protein binding rate of 55.4–59.8%. Its elimination half-life is 0.455 hrs. In healthy human volunteers, single instillations of ripasudil 0.4% have been associated with IOP reductions from baseline in a dose-dependent manner, with the maximum reduction reaching after 2 h.[8]

Ripasudil was approved by the Pharmaceuticals and Medical Device Agency (PMDA) of Japan on September 26, 2014, under the brand name Glanatec (ophthalmic solution 0.4%) as the world's first glaucoma drug with a Rho kinase inhibitory activity, and it was approved in 2019 in Korea. In India, ripasudil is a newer molecule for anti-glaucoma therapy after being launched on January 6, 2020.

The efficacy of monotherapy with ripasudil and of combination therapy using ripasudil and beta-blockers and/or PGAs has been reported in the literature.[11] However, the safety and efficacy of ripasudil administration as adjunctive therapy to the maximum medical therapy has been infrequently studied.[12] Herein, we report the results of our prospective analysis of the safety and efficacy of ripasudil added to the treatment regimen in patients with poorly controlled glaucoma under the maximum medical therapy, who would otherwise have required surgical intervention.

Methods

This prospective, randomized, interventional study was performed at a tertiary western regional institute of ophthalmology in India. Approval was obtained from the ethics committee to perform this study abiding by the tenets of the Declaration of Helsinki. All patients in this study were enrolled with written informed consent. The study period was from January 2021 to June 2021. Patients between 18 and 70 years of age presenting to our glaucoma clinic, diagnosed with primary open-angle glaucoma, compliant-adherent persistent with two or more anti-glaucoma medications but with inadequately controlled IOP were included in this study. The exclusion criteria were patients not willing to give consent, other types of glaucoma (angle-closure, mixed mechanism, pseudoexfoliation, pigment dispersion, secondary) having a history of previous glaucoma surgery and or laser treatment, having retinal pathology, pregnant females, exhibiting poor compliance or unwilling to come for regular and frequent follow-up. After inclusion, a thorough ophthalmic examination was done that included visual acuity assessment with Snellen's chart, slit-lamp biomicroscopic examination, tonometry using Goldmann applanation tonometer, gonioscopy with four mirror goniolens, and dilated fundus examination for retina and optic disc evaluation, visual field examination, pachymetry for corneal thickness, and diurnal variation test where necessary. We added ripasudil eye drops (0.4%) to be instilled twice a day as adjunctive therapy to the ongoing glaucoma treatment. On follow-ups at 7 days, 15 days, 1 month, 2 months, and 3 months, we assessed the visual acuity, IOP (mm Hg) with applanation tonometer, anterior segment, and the fundus. Safety assessment was also done on all follow-ups for tolerability and any adverse effects. The primary endpoint was the degree of IOP reduction at 3 months of treatment, whereas the secondary endpoints were the percentage of patients reaching the predefined target IOP and the incidence of adverse events. All the data were entered in a Microsoft excel sheet and analyzed. The IOP before and after use of ripasudil eye drops was compared by paired *t*-test. A P value < 0.05 indicates statistical significance. The safety of ripasudil was measured in percentage variation.

Results

Our study included 27 patients (total: 46 eyes), 18 of which were male and 9 were female. Among males and females, the maximum number of patients was above 60 years [Table 1]. Out of 27 patients, 19 patients were on more than 3 anti-glaucoma medications, 4 patients were on two anti-glaucoma medications [Table 2]. Out of 27 patients, ripasudil was started in 19 patients in both eyes, in the right eye (RE) in 3 patients only, and only in the left eye (LE) 5 patients [Table 3]. The mean pachymetry was 519.93 μm in RE and 523.86 μm in LE and the mean cup disc ratio was 0.8 in RE and 0.7 in LE.

Our study reported a statistically significant reduction in IOP at all time durations (P < 0.00001) with the maximum reduction at 3 months [Table 3, Fig. 1]. All patients (100%) in our study reached the predefined target IOP with ripasudil.

Table 1: Age distribution

Age	No of patients
<30	0
31-45	2
46-60	9
61-75	13
>75	3
Total	27

Table 2: Number of anti-glaucoma medications used by patients

Total no. of medications	RE	LE
≤2	4	4
3	11	11
4	7	8
≥5	1	1

Table 3: Intraocular pressure measurements through the study duration

	Mean IOP±SD		Difference from baseline		Comparison (paired test)		*T*	
	Right eye (mm Hg)	Left eye (mm Hg)	Right eye (mm Hg)	Left eye (mm Hg)	Right eye	Left eye	Right eye	Left eye
Baseline (mm Hg)	16.70±8.61	18.22±7.13	----	------	------	------	------	-----
7 days (mm Hg)	12.70±6.77	14.52±6.50	–4.0	–3.74	*P*=<0.00001	*P*=<0.00001	6.098	5.25
15 days (mm Hg)	12.30±6.74	13.96±5.86	–4.41	–4.26	*P*=<0.00001	*P*=<0.00001	6.365	7.12
1 month (mm Hg)	11.55±5.98	12.26±4.90	–5.15	–5.96	*P*=<0.00001	*P*=<0.00001	7.30	10.01
IOP at 2 month (mm Hg)	11.26±5.71	12.22±4.68	–5.44	–6.0	*P*=<0.00001	*P*=<0.00001	7.55	8.57
IOP at 3 month (mm Hg)	11.33±5.68	12.22±4.55	–5.37	–6.0	*P*=<0.00001	*P*=<0.00001	8.18	9.50

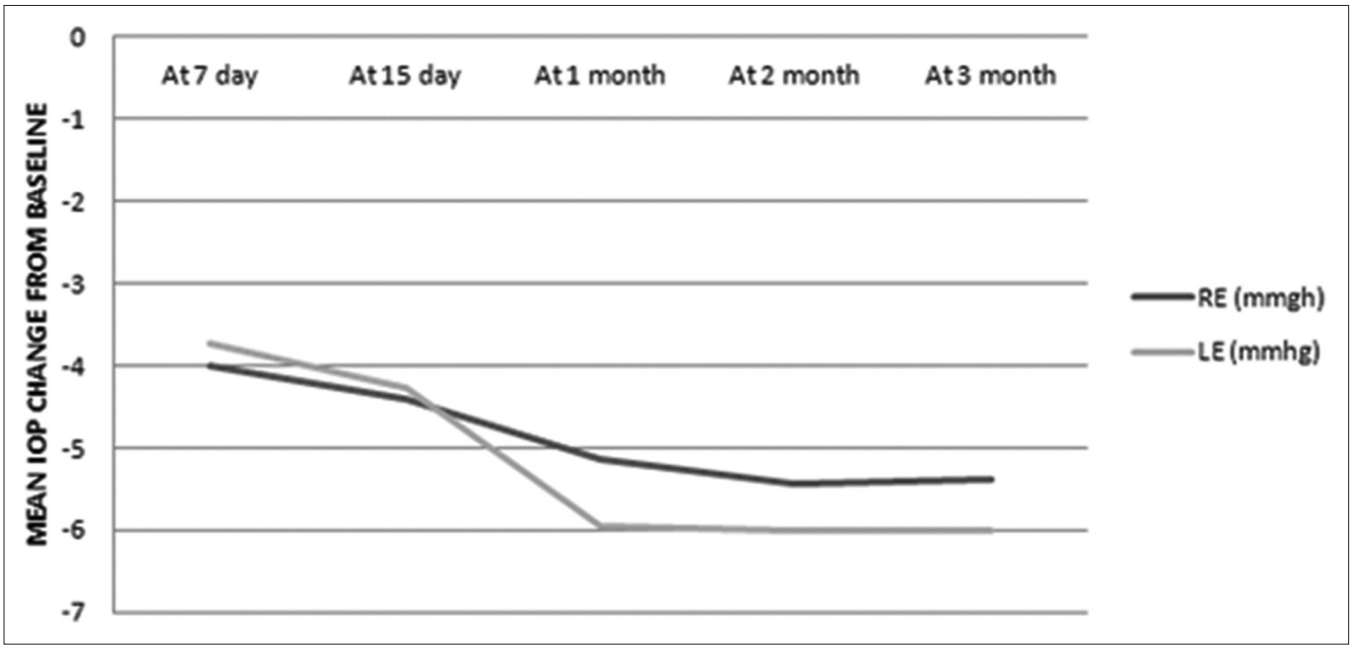

Figure 1: Mean IOP changes from baseline

In our study, 5 patients developed no adverse effects to ripasudil, and 22 patients had mild conjunctival hyperemia, which resolved within a few days. No patient developed any side effects necessitating the omission of ripasudil and or requiring any additional adverse event management.

Discussion

In this study, we demonstrated the additive IOP-lowering effects of ripasudil topical instillation along with other glaucoma therapeutic agents in varying combinations. Currently, PGAs, α1-blockers, and α2-agonists are used to promote uveoscleral outflow, whereas β-blockers and CAI are used to suppress aqueous humor production. In addition, these agents are selected according to the target IOP of each patient and patient and disease characteristics. However, there still remain unmet medical needs in the market for developing novel classes of ocular hypotensive agents, which would be equally efficacious, if not superior; be safe; and devoid of evident contraindications. In our study, we demonstrated a significant reduction in IOP in all patients at all time durations, the maximum being at 3 months of starting the drug. Sato *et al*.[12] reviewed 92 patients who received ripasudil as an additive treatment, comprising 43 patients with Primary Open Angle Glaucoma (POAG), 28 with Normal Tension Glaucoma (NTG), 10 with secondary glaucoma (SG), 7 with pseudoexfoliation glaucoma (XFG), and 4 with developmental glaucoma (DG). They reported that the mean IOP decreased from 18.9 mm Hg at baseline (n = 92) to 15.8 mm Hg at 6 months (n = 55). Kawara *et al*.[13] studied 116 consecutive ripasudil-treated patients (76 POAG, 31 SG, and 9 DG patients) and found that the median (interquartile range) 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. In our study, all patients having primary open-angle glaucoma showed a reduction in IOP in RE from baseline 16.70 mm Hg to 11.33 mm Hg and in LE from baseline 18.22 mm Hg to 12.22 mm Hg at 3 months, with this reduction being statistically significant (P < 0.00001). All patients reached a predefined target IOP at the end of the study (100%).

These results suggest that an increment of conventional outflow is effective for lowering the IOP under the increase in the uveoscleral outflow and reduced aqueous formation. Other studies also suggest that there is an additional benefit

of ripasudil for neuroprotection and improvement of ophthalmic perfusion. Nakabayashi *et al*.[14] reported that ripasudil increased the retinal blood flow in cats.[14] Similar results were reported by other ROCK inhibitor reagents, and this effect might be due to the direct vasodilating action of ROCK inhibitors in the posterior side of the eye.[15,16] The most common side effect of ripasudil is conjunctival hyperemia, followed by sub-conjunctival hemorrhage and cornea verticillata.[17] In our study, 5 patients had no adverse effects, 22 had mild conjunctival hyperemia, and none had any significant conjunctival hyperemia, suggesting an overall good safety profile of ripasudil.

The study limitations were a smaller sample size and short duration for follow-up. Nevertheless, substantial results could be elucidated that can help practitioners to define the position of this new molecule into the glaucoma medication armamentarium.

Conclusion

Accumulated evidence so far suggests that ripasudil is a promising anti-glaucoma drug that can lower IOP, irrespective of the glaucoma subtype and the pattern of treatment initiation. The addition of ripasudil to the existing maximal therapy exerted an additional IOP-lowering effect, mainly because the mechanism by which ripasudil lowers the IOP differs from that of other antiglaucoma medications. As regard safety, conjunctival hyperemia is the most common adverse event, is usually transient and mild and unlikely to be a reason for discontinuation, especially if the patient is pre-informed. Using it as an adjunctive therapy can avoid glaucoma surgery or delay it. Several ROCK inhibitors other than ripasudil are also being currently studied and or used clinically. More data from post-marketing studies will be required to establish the best practices for the treatment of patients with glaucoma or Occular Hypertension (OHT) using ROCK inhibitor ophthalmic solutions.

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Conflicts of interest

There are no conflicts of interest.

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