ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 02 | February - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

STUDY ON EFFICACY AND SAFETY OF RIPASUDIL HYDROCHLORIDE IN TREATMENT OF NEWLY DIAGNOSED PRIMARY OPEN ANGLE GLAUCOMA

Ophthalmology

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ABSTRACT

Aim: The study aims at evaluating the lowering effect of Intraocular pressure (IOP) and tolerability of Ripasudil(0.4%) ophthalmic solution, a selective rho kinase1 inhibitor, as monotherapy in newly diagnosed primary open angle glaucoma patients. **Background:** Glaucoma is a chronic progressive optic neuropathy causing irreversible blindness around the world. Current treatment strategy stems from concept of lowering IOP, which is a key modifiable risk factor. Ripasudil also known as K 115,is the world's first Rho-associated coiled-coil-containing protein Kinase 1(ROCK1) inhibitor that lowers IOP by directly acting on trabecular meshwork,increasing conventional outflow. **Methods:** This prospective, interventional study included 53 patients of newly diagnosed primary open angle glaucoma.0.4% Ripasudil ophthalmic solution was instilled twice a day as the primary treatment. The primary endpoint was the degree of IOP reduction after 6 months of treatment, whereas the secondary end points were percentage of patients reaching the predefined target IOP and incidence of adverse effects. **Results:** We examined 53 eyes of 53 primary open angle glaucoma patients. The IOP reduction (relative percentage IOP reduction)from baseline was -2.3 mm Hg(-1.7 to -2.9 mm Hg,95%confidence interval ,P<0.001).The predetermined target IOP was achieved by 54.7% population(29 among 53 patients).The most common adverse effects noted were conjunctival hyperaemia (54.7% of patients),allergic conjunctivitis(35.8% of patients) punctate keratitis(11.32% of patients), blepharitis(15.09% of patients), headache(24.5% of patients), bradycardia(9.43% of patients). **Conclusion:** Administration of 0.4% Ripasudil ophthalmic solution monotherapy revealed IOP lowering effect and acceptable safety profile in POAG patients. As ROCK inhibitors are novel anti-glaucoma drug, more data and studies are needed to establish best practices for the treatment of the patients.

KEYWORDS

Ripasudil, Monotherapy, IOP, Glaucoma, Efficacy

INTRODUCTION

Glaucoma is a group of disorders of chronic progressive optic neuropathy, characterized by functional and structural abnormalities of the optic nerve related to retinal ganglion cell death. It is the 2nd major leading cause of irreversible blindness around the world. The risk factors for the onset and progression of glaucoma are reported to be age, ethnicity, family history, myopia of a higher degree and increased intraocular pressure (IOP). Although the pathogenesis of glaucoma remains unclear,a consensus exists that death of retinal ganglion cells (RGCs)in a typical pattern is a key cellular event that leads to characteristic glaucomatous optic disc changes with associated visual field loss.[1]Most common single form of glaucoma worldwide is Primary open angle glaucoma(POAG)[2].Slowly progressive raised IOP (>21mm Hg recorded at least a few occasion)contributes as main risk factor.Current treatment strategies stem from the concept of lowering intraocular pressure (IOP),based on major randomized controlled trials showing the protective effect of IOP lowering on visual field progression in glaucoma eyes[3].Many classes of antiglaucoma medications, including prostaglandin analogs(PGs) and b-blockers, are currently available. Nevertheless,glaucoma cannot often be successfully controlled even withthe use of these medications,Therefore, antiglaucoma medications with novel mechanisms of action are being sought.Ripasudil Hydrochloride Hydrate,first introduced in the market in Japan,December 2014,also known as K-115,is a novel antiglaucoma drug which is world's first Rho-associated coiled-coil-containing protein kinase (ROCK)inhibitor eye drop that lowers IOP by increasing conventional aqueous outflow through the trabecular meshwork and Schlemm's canal[4].Rho kinase is a serine/threonine protein kinase involved in the modulation and regulation of cell size and shape by acting on cytoskeleton. ROCK is an important downstream effector of Rho guanosine triphosphates(GTP),proteins that are significant in contractile control of smooth muscle tissue[5].several ex vivo and in vivo experiments demonstrated conventional outflow tissue responses to ROCK inhibitors: increased aqueous humor outflow[6],expanded outflow route[7]and suppression of the fibrogenic response[8].Herein, we report the results of our prospective analysis of the safety/efficacy of Ripasudil eyedrop as monotherapy in newly diagnosed POAG patients.

MATERIALS AND METHODS

We conducted a prospective, interventional,case series study at Glaucoma Clinic,N.R.SMedical College and Hospital. Enrolment for this study was started in January 2020 and was scheduled to be completed at June 2020.The study was approved by the Institutional Review Board of our centre. All the participants received complete information regarding the study protocol, and written informed consent was obtained from each of the participants before he/she was enrolled in the study.The inclusion criteria were as follows: patients with primary open angle glaucoma (POAG) irrespective of gender, 20 years of age or older. We fixed the target IOP at 16-18mm Hg after 6 months of treatment. The exclusion criteria were as follows: narrow angles as assessed by gonioscopy,defined as grade 2 or less according to the Shaffer[9], and the presence of secondary or traumatic glaucoma. We also excluded patients with a history of ocular surgeries, including cataract surgery within the previous year; glaucoma surgery, retinal laser treatment, selective laser trabeculoplasty, or Nd: YAG laser posterior capsulotomy within the previous 90 days; and eyelid surgery within the previous 120 days.The patients were instructed not to take corticosteroids,not to change the dosages of any drugs they were on that may affect the IOP, and not to wear contact lenses. One drop of Ripasudil 0.4% was instilled into the target eye twice daily, at 8 AM and 8 PM, for 6 months. We investigated the IOP-lowering effect of Ripasudil and the incidence of adverse events associated with instillation of Ripasudil after each month of treatment.The IOP was measured using a Goldmann applanation tonometer at every visit. To evaluate the safety of Ripasudil instillation,we carried out ophthalmologic examinations,where we examined the eyelids, palpebral and bulbarconjunctivae,cornea,anterior chamber, iris, and lens by using slit-lamp microscopy along with visual acuity testing,fundus examination by 90D lens, and visual field examination and general systemic examination.We calculated the changes in the IOP (relative percentage of IOP reduction)after 6 months of treatment from baseline,at time-matched points&used it as the primary end point.The secondary end points were the percentage of patients in whom the predefined target IOP was achieved, as well as the incidence of adverse events.we analysed the subgroups by dividing baseline IOP for subjects with ≥23 mmHg and <23 mmHg. Adverse effects were classified into local and systemic adverse effects.

Statistical Analysis:

Statistical analysis of the differences in the IOP between different follow-up dates was performed using the 2-tailed Paired t test.The

statistical significance level was set at P<0.05 and the 95% confidence intervals (CIs) were calculated for the IOP differences. The IOP values were expressed as the means±SD.

RESULTS

33 patients had completed treatment as advised and timely followed up, but 20 patients could not continue complete follow up due to non-availability of transportation due to nationwide Covid-19 Pandemic lockdown. The baseline characteristics of the patients are shown in Table 1.None of the patients changed any medications or took oral carbonic anhydrase inhibitors, pilocarpine, or similar miotics during the study period

Table 1: Demographic characteristics of patients.

CHARACTERISTICS	VALUE
No. of eyes examined	53
Male	20(37.73%)
Female	33(62.26%)
Age (Mean±SD) Y	45±10.6
Baseline IOP in affected eye (Mean±SD) mmHg	25.09±3.93
Laser trabeculectomy	0
Iridectomy	0

The mean IOP values after 4,8,12&24 weeks of treatment are shownin Table 2. Figure1 showing the differences in intraocular pressure (IOP) relative to the baseline value after 4,8,12&24 weeks of use.

Table 2: showing progressive reduction of IOP over time

Subgroup	Examination time	IOP reduction Mean(SD)mm hg	Relative % IOP reduction
a	4 weeks	-0.72(1.02)	-6.4
	8 weeks	-1.5(2.3)	-7.6
	12 weeks	-4.1(1.8)	-18.1
	24 weeks*	-5.1(1.4)	-23.9
b	4weeks	-2.2(1.2)	-8.0
	8weeks	-4.2(1.9)	-15.5
	12weeks	-7.0(1.8)	-25.7
	24 weeks*	-7.9(2.1)	-29.6

Subgroup a=IOP <23 mm Hg, Subgroup b=IOP≥23 mmHg

*as some patients could not complete thorough follow up for the last 3 months due to Covid-19 lockdown.& we got all patients on 24 weeks for follow up.

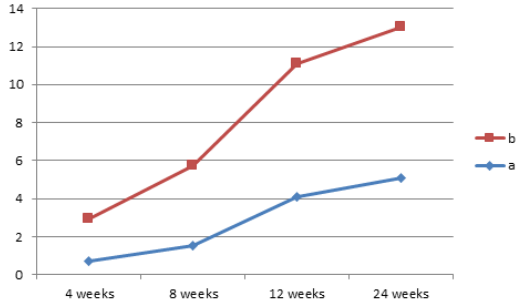

Figure-1 showing progressive reduction of IOP over time(y axis denotes absolute reduction of IOP(ΔIOP) ,x axis denotes duration of treatment in weeks).Group a=changes of subgroup a, Group b=changes of subgroup b.

These reductions after 24 weeks of treatment were all statistically significant, p<0.0001. The predefined target IOP at the end of 6 months of treatment was achieved in 54.7% (29/53) of the patients.

Table 3: Adverse effects of topical Ripasudil treatment

Adverse effects	No. of patients
LOCAL:	
Conjunctival hyperemia	29(54.7%)
Allergic conjunctivitis	19(35.8%)
Punctate keratitis	6(11.32%)
Blepharitis	8(15.09%)
SYSTEMIC:	
Headache	13(24.5%)
Bradycardia	5(9.43%)

Table-3 lists the adverse events observed in >2 patients in this study. The most frequent adverse event was conjunctival hyperemia, found on 29 patients (54.7%).

The adverse effects were categorized into mild, moderate and severe grades. The hyperemia was mild, but occurred after every instillation and persisted for about 2 hours. In all patients, the hyperemia disappeared by about 2 hours after the instillation. Most side effects were in mild grade. In all of these patients, the adverse events resolved without any additional medical treatment. The ocular examination findings revealed no clinically relevant changes.

DISCUSSION

In this study, we demonstrated the significant IOP lowering effect of Ripasudil administered as monotherapy in patients with newly diagnosed POAG.The degrees of IOP reduction following monotherapy with Ripasudil for 4,8 weeks and 12 weeks were -3.5mm Hg (6.4%),-4.1 mm Hg(7.6%),-5.3 mmHg(18.1%) respectively for subgroup a (IOP<23mm Hg);for subgroup b(IOP≥23 mmHg) the degrees of IOP reduction for 4,8&12 weeks were -2.2mm Hg(8.0%),-4.2 mmHg(15.5%) &-7 mm Hg(25.7%).The mean additive IOP reduction obtained with Ripasudil instillation in monotherapy was-1.7 to 2.9 mm Hg.Among the 53 patients, however 20 failed to follow up during the lockdown due to COVID pandemic. All 53 patients were reviewed again at 24 weeks. The degree of IOP reduction for 24 weeks were -5.1mm Hg (23.5%) for subgroup a and -7.9mm Hg (29.6%) for Subgroup b. A previous study of Tanihara, Inoue et al showed The mean IOP reductions at trough and peak at 8 weeks 3.2 &2.2 mm Hg;at 52 weeks were -2.6 and -3.7mm Hg respectively for monotherapy.[10] Clinical trial, phase III, JapicCTI-111564 Multicenter, randomized, doublemasked, parallel group comparison studies showed Ripasudil (monotherapy) at 8 weeks the mean IOP reductions were -4.0mm Hg&-2.9mm Hg at peak& trough respectively.[11]The IOP continued to decline throughout the 6-months study period. We considered 2 hypotheses to explain this continuing decline. First, Ripasudil induces retraction and rounding of cell bodies, as well as disruption of actinbundles in the trabecular meshwork cells. It decreases transendothelial electrical resistance and increases the transendothelial flux.[12] We think that the IOP continued to decline during the study period because it takes a few months for the intraocular distribution of ripasudil to stabilize. Second, ocular hypertension is known to be caused by the accumulation of the extracellular matrix in the trabecular meshwork, which increases the resistance to aqueous outflow through the trabecular pathway. Pattabiraman et al[8] reported that a rho-kinase inhibitor decreased the extracellular matrix accumulation in the trabecular meshwork, and this phenomenon might explain the IOP reduction obtained with this class of drugs. Because it takes a few months for a rho-kinase inhibitor todecrease the extracellular matrix accumulation, the IOP continued to decline during the study period. From the viewpoint of the safety, There was a high incidence of conjunctival hyperemia observed; however, most of those findings were mild, transient, and resolved spontaneously, which agrees with the findings in previous short-term studies (Tanihara et al. 2013a,b, 2015) and other Rhokinase inhibitors (Tanihara et al. 2008;Williams et al. 2011).Ocular hyperemia evidently resulted from smooth muscle relaxation of the blood vessels, because rho-kinase inhibitors induce vasodilatation[13] .With regard to other adverse events, allergic conjunctivitis and punctate keratitis occurred in 35.8% (19/53) and 11.32% (6/53) of the patients, respectively. Study by Inazaki et al revealed conjunctival hyperemia in 100% patients, followed by allergic conjunctivitis in 2 patients (5.6%),punctate keratitis in 2 patients (5.6%)[11].Another study by Tanihara,Inoue et al showed conjunctival hyperemia in 70.7% patients, followed by blepharitis in 25%patients, allergic conjunctivitis in 20.2% patients.[10]But none of the patients discontinued their study treatment due to the adverse effects. Thus, Ripasudil appears to be safe even when used with maximum medical therapy.

However, our study had the limitation that the follow-up period was short. The efficacy of long-term treatment with the drug remains unknown. As some of the patients could not continue follow up throughout all of the study period due to problems of transportation due to nationwide lockdown because of COVID 19 pandemic, we could not fetch more accurate results. Thus, further investigation of IOP-lowering effect of long-term Ripasudil therapy as monotherapy as well as adjuvant therapy is warranted.

CONCLUSION:

The use of Ripasudil in newly diagnosed POAG patients might significantly lower the IOP, and may help avoid glaucoma surgery, at least in the short term. This was confirmed by our finding that 54.7%

(29 among 53 patients) of the participating patients showed an IOP reduction to the predefined target value after the Ripasudil monotherapy of 6 months. Although conjunctival hyperemia was encountered as an annoying side effect in most patients, the drug was otherwise well tolerated.

DISCLOSURE:
Funding: No funding sources
Conflict of interest: none declared.

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