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Assessment of Effect and Safety of Ripasudil (0.4%) in patients of Primary Open Angle Glaucoma / Ocular Hypertension

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Abstract

Background: The aim is to evaluate the intraocular pressure-lowering efficacy and tolerability of Ripasudil (0.4%) ophthalmic solution in patients of primary open-angle glaucoma/ocular hypertension. **Material & Methods:**In this prospective, interventional, single-arm, open-label study, 50 patients of POAG/ocular hypertension attending the Outpatient Department of Ophthalmology, Government Medical College, Patiala were included. **Results:** Mean value of numerical change in IOP at four weeks, at eight weeks, at twelve weeks in IOP were 3.61 ± 2.05, 3.98 ± 1.47, 4.44 ± 1.53 respectively. Among side effects, conjunctival hyperemia, blepharitis, and allergic conjunctivitis were reported among 62%, 10%, and 8% of the subjects at four weeks. Final results after 12 weeks showed that only conjunctival hyperemia was reported as a side effect among 16% of the subjects. **Conclusions:** Our present study showed significant IOP-lowering effects and safety of ripasudil (0.4%) over 12 weeks in patients with primary open-angle glaucoma/ocular hypertension. For the treatment of glaucoma and OHT, ripasudil is regarded as a possible second-line choice in spite of the high occurrence of conjunctival hyperemia.

Keywords:-Ripasudil, IOP, Conjunctival Hyperemia.

INTRODUCTION

Glaucoma, a progressive degenerative optic neuropathy, causes characteristic loss of visual field and is characterized by functional and mechanical abnormalities of the eyes (i.e., death of retinal ganglion cells and related optic nerve damage).[1] One of the primary causes of irreversible blindness in the world is Glaucoma.[2] Between 64 - 70 million people are affected worldwide by glaucoma, according to estimates published in 2014.[3] Since this condition is associated with an increase in age,the estimated rise in prevalence of glaucoma is 76 million in 2020 and more than 111 million by 2040.[4] Primary glaucoma is often classified into two broad categories depending upon the type of angle formed between iris and cornea (wide and open-angle or closed/narrow-angle) that is primary open-angle glaucoma (POAG) and primary angle-closure glaucoma.[2]

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Ocular hypertension (OHT) is a pathological condition with normal optic nerve and visual field despite elevated IOP. Various studies have reported that in patients with POAG with elevated IOPs and with NTG,[5] every IOP's millimeter reduction is significant in delaying the disease progression.[6] Hence the main goals of glaucoma treatment are to slow disease progression and the only proven treatment approach is to reduce intraocular pressure (IOP).[4,7] There are various pharmacotherapies that lower IOP by either increasing uveoscleral outflow or decreasing aqueous humor production without specifically targeting the diseased TM pathway.[8,9] Prostaglandin analogs are often recommended first-line therapy because of the overall safety, tolerability, efficacy profile, and once-daily (OD) administration. However, characteristic cosmetic adverse reactions, such as eyelid and iris pigmentation, elongation of the eyelashes, and deepening of upper eyelid sulcus occur as a result of prostaglandin use. Beta-blockers, which are positioned after prostaglandin analogs, have contraindications based on the systemic (e.g., cardiovascular and pulmonary) adverse drug reactions and thus have a significant drawback in treating elderly patients with glaucoma who often have cardiovascular and respiratory comorbidities.[2]

There is still a need to have more drugs, especially drugs that have an effect via a new mechanism of action. Ripasudil, K-115, is a Rho kinase inhibitor with significant IOP lowering effects by modulating the conventional aqueous outflow pathway (Isobe et al. 2014).[10,11]Ripasudil (i.e., GlanatecR Ophthalmic Solution 0.4%; Kowa Co., Ltd., Nagoya, Japan), a new class of antiglaucoma medications, has been shown to lower IOP by modulating the cytoskeleton and focal adhesions in trabecular meshwork (TM) cells. Moreover, it has been reported that the actin cytoskeleton plays an essential role in regulating AH outflow in the TM outflow pathway,[12,13] and that ROCK inhibitors decrease resistance in the TM outflow pathway and reduce IOP.[14]

MATERIAL AND METHODS

In this prospective, interventional, single-arm, open-label study, 50 patients of POAG/ocular hypertension attending the Outpatient Department of Ophthalmology, Government Medical College, Patiala were included. The patients fulfilling the inclusion criteria and not presenting with any exclusion criteria were enrolled in the study. Proper consent was taken from the patients. Inclusion and exclusion criteria are as follows:

Inclusion Criteria:

1. Age should be > 18 yrs.
2. Diagnosed unilateral/bilateral primary open angle glaucoma /ocular hypertension cases.
3. IOP responsive to but insufficiently controlled by other drugs.
4. Baseline IOP > 18mm Hg but < 28mm Hg in at least one eye.
5. Patients who are willing to get enrolled in the study.
6. No observable signs of ocular surface disease.

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Exclusion Criteria:

1. All patients with an established diagnosis of secondary glaucoma or angle-closure glaucoma.
2. Ocular inflammation.
3. Ocular infection.
4. Pregnant and lactating females.
5. Patient unable to attend follow-up.
6. Any known sensitivity to study drugs.
7. H/O intraocular surgery within six months before the study.
8. Patient with IOP >28 mmHg

Study Eye

In the study group, one eye (the affected eye) fulfilling the inclusion criteria was considered the study eye. If both eyes have glaucoma, both eyes were treated, but only one eye was studied.

Ethical clearance:

The study protocol for all procedures was approved by the Institutional Review Board for Ethical Clearance of Government Medical College, Patiala was included and performed in accordance with the Code of Ethics of the World Medical Association according to the Declaration Helsinki of 1975, as revised in 2000. Informed and written consent was obtained from all the patients prior to the commencement of the study.

Case selection:

The questionnaire was conducted to obtain the pretested data with modifications made prior to its use in the study. The patients were interviewed and requested the demographic, socioeconomic status, medical history, and previous history of taking any medications and supplements.

Study Sequence

Study design:

This was a prospective, interventional, single-arm, open-label study.

Sample size:

Fifty patients of POAG were selected after fulfilling the inclusion criteria. Informed consent was taken from the patients included in the study. In addition, demographic data, detailed ocular, and medical history were noted, and the past treatment history as per the proforma.

Study drugs:

The patients were instilled one drop of Ripasudil (0.4%) ophthalmic solution at 8:00 a.m. and 8:00 p.m. for 12 weeks.

Iop measurement:

IOP readings were taken with the Goldmann applanation tonometer at each visit.

1. IOP on day 0 was measured before adding the ripasudil (0.4%) ophthalmic solution, as baseline IOP at 8:00 a.m., 10:00 a.m., and 4:00 p.m.
2. On subsequent visits of 3 months follow-up time, IOP was measured at 8:00 a.m., 10:00 a.m., and 4:00 p.m.

- Clinical evaluation of each patient on each visit during treatment was done as:

- History: Any subjective symptoms.

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- Intraocular pressure with Goldmann Applanation Tonometer.
- Any side effects.
- Both direct and indirect ophthalmoscopy.
- Slit Lamp examination.
- Slit Lamp Biomicroscopy with 78 D/90 D.
- Perimetry at 12 weeks.

Methodology

A detailed ocular and medical history were obtained. A careful general physical examination was done to rule out any contraindications to the drugs.

Ocular examination was done as follows:

1. Best-corrected visual acuity (BCVA) was done with a Snellen chart.
2. Examination of lids, adnexa and lacrimal apparatus was done using diffuse light.
3. Direct ophthalmoscopy and slit lamp indirect biomicroscopy with +78D or +90D lens was done
4. Goldmann applanation tonometry: was used to measure intraocular pressure (IOP).
5. Perimetry (24-2 SITA Standard).

RESULTS

The present prospective, interventional, single-arm, open-label study was conducted among 50 patients of POAG/ocular hypertension. 17(34.00%) patients belonged to age group 61-70 years followed by 51-60 years (12(24.00%)), 41-50 years (9(18.00%)) and >70 years (7(14.00%)). The age group was 31-40 years of only 5 out of 50 patients (10.00%). Mean value of age (years) of study subjects was 58.94 ± 13.6. It is shown in [Table 1]. 30(60.00%) patients were males, and 20(40.00%) patients were females.The mean value of numerical change in IOP at four weeks, at eight weeks, at twelve weeks and percentage change in IOP at four weeks, at eight weeks, and twelve weeks of study, subjects were 3.61 ± 2.05, 3.98 ± 1.47, 4.44 ± 1.53, 14.46 ± 8.37, 15.89 ± 6.04 and 17.71 ± 6.33 respectively. It is shown in [Table 2 and Figure 1] respectively.

At four weeks, conjunctival hyperemia, blepharitis, and allergic conjunctivitis were reported among 62%, 10%, and 8% of the subjects. Finally, after 12 weeks, only conjunctival hyperemia was reported as a side effect among 16% of the subjects. It is shown in [Table3].

Table 1: Distribution of age(years) of study subjects.

Age(years)	Frequency	Percentage
31-40	5	10.00%
41-50	9	18.00%
51-60	12	24.00%
61-70	17	34.00%
>70	7	14.00%
Mean ± SD	58.94 ± 13.6	
Median(25th-75th percentile)	60(50-68)	
Range	31-87	

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Table 2: Descriptive statistics of IOP change after treatment at various intervals of study subjects.

IOP change after treatment at various intervals	**Mean ± SD**	**Median(25th-75thpercentile)**	**Range**
Numerical change at 4 weeks	3.61 ± 2.05	3(2.667-3.667)	0-11.33
Numerical change at 8 weeks	3.98 ± 1.47	3.4(3.367-4.7)	0.33-9
Numerical change at 12 weeks	4.44 ± 1.53	4(3.667-5.058)	2-9.33
Percentage change at 4 weeks	14.46 ± 8.37	12.2(10.256-15.152)	0-47.22
Percentage change at 8 weeks	15.89 ± 6.04	14.2(12.169-19.797)	1.22-34.62
Percentage change at 12 weeks	17.71 ± 6.33	15.6(13.253-21.28)	7.14-38.36

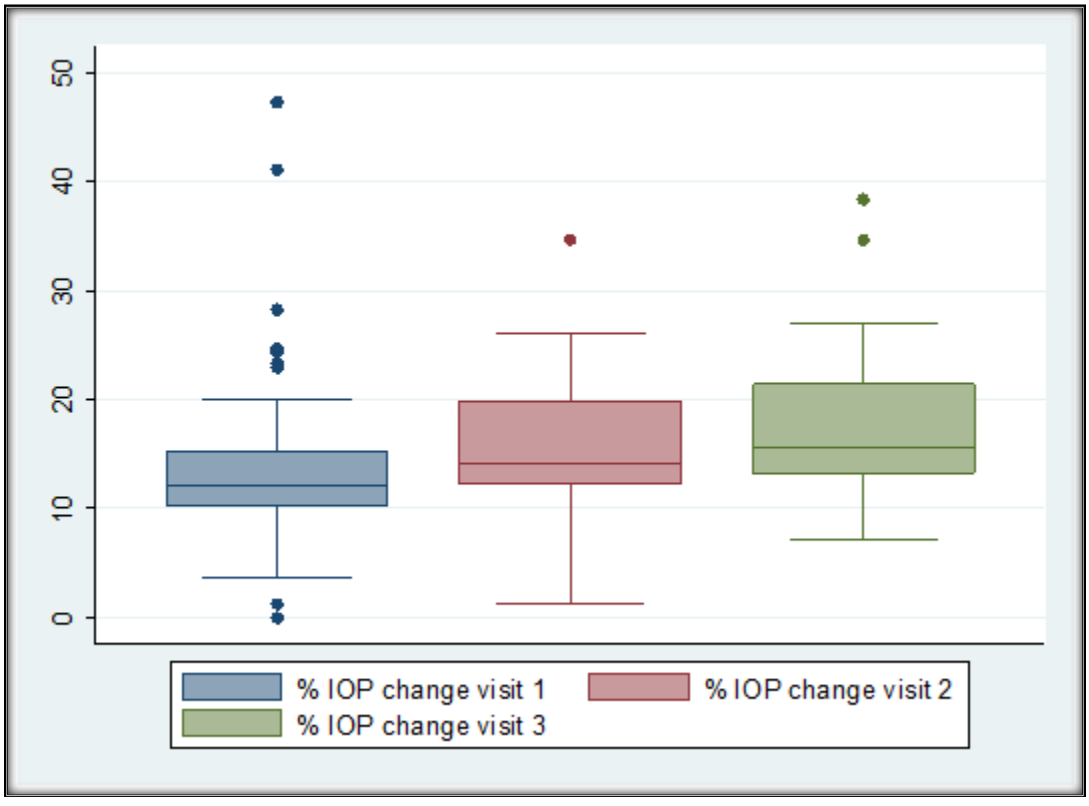

Figure 1: Descriptive statistics of percentage change in IOP at four weeks, eight weeks, and twelve weeks of study subjects.

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Table 3: Side effects among the study subjects at different intervals

IOP	Conjuctival hyperemia		Blepharitis		Allergic Conjunctivitis		p-value
	N	%	N	%	N	%	
4 Weeks	31	62	5	10	4	8	<0.01**
8 Weeks	26	52	3	6	1	2	
12 Weeks	8	16	0	0	0	0	

**: highly significant

DISCUSSION

Glaucoma is the leading cause of irreversible vision loss in adults worldwide. Reportedly, an increase in intraocular pressure (IOP) is the primary risk factor for thedevelopment and progression of glaucoma. Thus, the most effective treatment for glaucoma is lowering the increased IOP. Recently, many new antiglaucoma eyedrop medications have been developed and approved for use in Japan, including omidenepagisopropyl (a selective EP2 agonist), ripasudil hydrochloridehydrate [a rho-associated protein kinase (ROCK) inhibitor], and brimonidine tartrate (an alpha-2 adrenergic agonist), thus providing clinicians with a wider option of eyedrop medications that can be selected for treatment.[14]

The present prospective, interventional, single-arm, open-label study was conducted among 50 patients to find out the intraocular pressure-lowering efficacy of Ripasudil (0.4%) ophthalmic solution in patients of primary open-angle glaucoma/ocular hypertension and to evaluate the tolerability of Ripasudil (0.4%) ophthalmic solution in patients of primary open-angle glaucoma/ocular hypertension. Out of 50 subjects, 30 (60%) were males and 20 (40%) were females in this study. Mean value of age(years) of study subjects was 58.94 ± 13.6 The proportion of patients with early glaucoma was significantly higher in 41-50 years (55.56%), 51-60 years (50%). The proportion of patients with moderate glaucoma was significantly higher in >70 years (100%) and 61-70 years (82.35%). The severity of glaucoma increased with age of the persons. Increasing age has also been predicted as an important risk factor for development of blindness due to progression of glaucoma.[15]

The mean IOP at baseline, four weeks, eight weeks, and twelve weeks was 25.25±1.7, 21.64±2.88, 21.27±2.43, and 20.82±2.45, respectively. Hence after the intervention, the IOP levels decrease at different intervals. In the present study, majority (35(70.00%)) of patients, the 2nd drug addition was not required. The addition of 2nd drug was required in only 15 out of 50 patients (30.00%) suggesting that the IOP-lowering effect of ripasudil as monotherapy was significant. At four weeks, conjunctival hyperemia, blepharitis and allergic conjunctivitis were reported among the subjects of 62%, 10%, and 8%. After twelve weeks, only conjunctival hyperemia was reported as a side effect, and that too among 16% of the subjects in the present study.

CONCLUSIONS

In conclusion, our present study showed significant IOP-lowering effects and safety of 0.4% ripasudil over 12 weeks in patients with

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primary open-angle glaucoma/ocular hypertension. Our present data suggest that a potential side-effect after long-term use is an inflammatory reaction. For the treatment of glaucoma and OHT, ripasudil is regarded as a possible second-line choice in spite of the high occurrence of conjunctival hyperemia.

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