Original Article

Comparative Analysis of Efficacy & Safety of Prostaglandin - Timolol Fixed Combination *versus* Adding Ripasudil to Prostaglandin in Primary Open Angle Glaucoma Patients with Insufficient IOP Control with Prostaglandin Analogue Monotherapy — An Open Label, Randomised Study

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Purpose : To compare the efficacy & safety of either switching from topical Prostaglandin analogue monotherapy to topical Prostaglandin – Timolol fixed combination therapy or adding Ripasudil to Prostaglandin monotherapy in Primary Open Angle Glaucoma (POAG) patients with insufficient intraocular pressure control.

Methods : 36 POAG patients, experiencing insufficient IOP control while on a Prostaglandin analogue were enrolled for this study.The participants were divided into 2 treatment groups- PG/ Timolol fixed combination group (switched group) & Ripasudil 0.4% eye drop (added group). Blood pressure, IOP, pulse rate were measured at baseline, 2weeks, 1month, 2 months & 3 months of study. AP (24-2) test was done in all patients at baseline & at 3 months of the study. Data on adverse drug reactions & IOP were collected and analysed on first 3 months of treatment.

Results : In the switched group mean IOP after 3 months was 17.3±2.73 mm hg & 16.88±3.01mm hg in the added group, both of which were statistically significantly lower than baseline (switched group 19.55±3 mm hg & added group 19.29 ±3.13 mm hg). At 3 months IOP was reduced by 2.22±0.85 mm hg (11.38±4.04%) in the switched group & 2.41±0.77 mm hg (12.63±4.22%) in the added group. After 3 months of the study there was no significant change in systolic & diastolic BP & pulse rate in either of the groups. In the switched group 4 (22.22%) & in the added group 6 (35.29%) participants experienced adverse reactions.

Conclusion : In POAG patients on prostaglandin monotherapy with insufficient IOP control, adding Ripasudil was equally safe & effective to switching PG/ Timolol fixed combination in reducing IOP after 3 months of treatment.

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Key words **: Prostaglandin-Timolol fixed combination, Ripasudil, Intraocular pressure.**

Glaucoma is the second leading cause of blindness globally, accounting for 12.3% of the total blindness. WHO has estimated that glaucoma caused blindness to around 4.5 million people. In India, glaucoma is the leading cause of irreversible blindness with at least 12 million people affected and nearly 1.2 million people are blind from it[1]. Population based studies report a prevalence between 2 to 13%. Every eighth individual aged 40 years or above has glaucoma or is at risk in India. Among them, 74% have open angle glaucoma. From 2010 to 2020, the most detectable change in glaucoma worldwide will be an increase of the incidence of glaucoma in India.

Editor's Comment :

- Ripasudil is a new drug in the glaucoma armamentarium.
- With a novel mechanism of action and minimum systemic side effects it is showing promising results.
- It can be a safe & effective adjunct to Prostaglandin analogues in POAG patients.

Primary Open Angle Glaucoma (POAG) is the commonest form of glaucoma throughout world, accounting for about two-thirds of cases. Today for OAG, both pharmacologic and surgical treatment modalities are aimed at lowering IOP, which is the primary modifiable risk factor associated with glaucoma progression[2]. Despite the availability of the therapies and the newer surgical treatments of glaucoma, two variants of OAG—progressive POAG (despite achieving "target" IOPs) and NTG—are the main challenges. Progressive POAG is characterized by

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significant visual field loss and increased likelihood of glaucoma progression despite multiple medications, often combined with laser or surgical interventions.

The antiglaucoma agents act on the aqueous humor dynamics to reduce the intraocular pressure by various mechanisms. Miotics in angle closure glaucoma act by contraction of sphincter pupillae, which removes papillary block and reverses obliteration of the iridocorneal angle & in open angle glaucoma act by contraction of the ciliary muscle pulls on the scleral spur and improves trabecular patency. β-blockers and carbonic anhydrase inhibitors reduce aqueous humor secretion by the ciliary body. Prostaglandins increase uveoscleral outflow by changing the permeability or pressure gradients[3]. Prostaglandins reduces IOP by facilitating the aqueous outflow through the uveoscleral pathway. It is thought that they bind to the receptors of the ciliary body and upregulate the matrix metalloproteinases. By remodelling the extracellular matrix these enzymes make the area more permeable to aqueous humor, thereby increasing outflow[4].

Commonly prostaglandins are the drug of first choice but when a single therapy of prostaglandin is not sufficient to lower the IOP, a combined treatment is indicated. While selecting an agent for combination therapy, we should think of the drugs with complementary mechanisms of action. Fixed-combination products have the combined efficacy of two ocular hypotensive drugs and the convenience of a two-drug regimen in a single container, which is beneficial for treatment adherence. Studies show that around 30% patients on Prostaglandin require additive therapy. Compared to a prostaglandin monotherapy, the range of IOP reduction in various PG- Timolol combinations from baseline is around 13-37%[5].

Recently, new addition to these IOP-lowering drugs, Rho-associated protein kinase (ROCK) inhibitors are showing promising result. They work by changing the status of trabecular meshwork and Schlemm's canal endothelial cells. They inhibit the contractile tone of actin cytoskeleton, resulting in improvement in the conventional aqueous outflow. Because of these novel IOP-lowering mechanisms, different from the mechanisms of action of other anti-glaucoma drugs, ROCK inhibitors are showing promises to investigators. In addition they protect trabecular meshwork from oxidative stress, improve optic nerve head blood flow, facilitate corneal endothelial wound healing, increase ganglion cell survival & reduce scarring in glaucoma surgery[6].

Ripasudil (0.4%), a derivative of Fasudil, approved as an antiglaucoma agent for the first time in September, 2014 in Japan, is now available in Indian market also. It is a selective Rho-associated coiled-coil-containing protein kinase1(ROCK1) inhibitor, where ROCK1 is an important downstream effector of Rho guanosine trisphosphates (GTP), proteins that are significant in the contractile control of smooth muscle tissue. The S configuration at the 2 position on the 1,4-diazepane ring of Ripasudil is responsible for its characteristic effect. Ripasudil hydrochloride hydrate showed no binding affinity for receptors of the adrenergic, endothelin, angiotensin II, glutamate, histamine, muscarinic or prostanoid variety. It doesn't have any affinity for Ca+&K+ channels,HMG-Co A reductase, carbonic anhydrase. Ripasudil had no effect on respiratory or neurological function. It is believed to be non-carcinogenic due to its rapid elimination, as well as it lacks inflammatory response in the eye post-administration[7].

Ripasudil has shown IOP-lowering effects when used as monotherapy or in combination therapy with prostaglandin analogues or beta-blockers. In addition to it Ripasudil has a comparatively good safety profile in relation to the adverse drug reactions (ADRs). Commonly switching patients from PG to PG/Timolol FC therapy leads to a good patient compliance. There is proven literature support that both PG/Timolol FC eye drops and PG eye drops with Ripasudil (0.4%) eye drops cause safe & effective reduction of IOP.

Materials and Methods

This is a prospective, open-label, randomised comparative study investigating the safety and efficacy of either switching from topical PG analogue monotherapy to topical PG/Timolol fixed combination therapy or adding Ripasudil (0.4%) drops in patients with primary open angle glaucoma who had insufficient IOP control while on PGA monotherapy, done in a tertiary eye hospital in Kolkata, West Bengal. The total surveillance period for this study is from March, 2020 to August, 2020.

Patients were eligible to participate if they had primary open angle glaucoma & IOP control was insufficient with PG monotherapy for more than 3 months & had not previously received Ripasudil treatment. The data of interest included patient background, study treatment status, concomitant medication status, ocular surgery status, ophthalmic parameters (eg, IOP, visual field and corrected visual acuity and detailed slit lamp examination) and ADRs on all follow up visits. All the participants gave written informed consent before participation & the study was done in accordance with the tenets of the Declaration of Helsinki.

Inclusion criteria :

(1) Male & female patients aged 40-75 years of age

(2) POAG patients having insufficient IOP reduction after more than 3 months of treatment with PG analogue

(3) In cases where both eyes qualified for study inclusion, the eye with higher IOP was selected. If both eyes had same IOP, then the right eye was selected for the study.

Exclusion criteria :

(1) Patients having serious systemic illness (eg. Asthma, allergy, cardiac illness)

(2) Patients having history of drug hypersensitivity were excluded

(3) Subjects with advanced cases of Glaucoma, central visual field loss in either eye measured by perimetry

(4) Subjects who are blind in one eye

(5) Subjects who are scheduled to undergo any kind of eye surgery during the study period

(6) History of chronic, recurrent or severe inflammatory eye diseases (eg, scleritis, uveitis, keratitis) or current other severe ocular pathology such as diabetic retinopathy, retinal detachment, severe dry eye

(7) Subjects using the listed medications were excluded from the study- (a) oral antihypertensive agents, (b) systemic steroids or immunosuppressive agents, (c) high dose (>1 gm daily) of salicylates

In this study we included total 36 patients (20 men,16 women, total 36 eyes) with POAG who were being treated with PG analogue monotherapy administered daily at 9 PM at night. Among them 8 eyes Latanoprost, 10 eyes Travoprost and 18 eyes were using Bimatoprost as PG monotherapy and IOP reduction was insufficient after more than 3 months of treatment. The participants were randomly placed into one of the two groups -(1)switch from once daily PG monotherapy to PG/Timolol fixed combination therapy administered in the evening at 8 pm(switched group) or (2) addition of twice daily Ripasudil (0.4%) in the morning 8am & in the evening 8pm to once daily PG analogue monotherapy at 9 pm (added group).

In the switched group Latanoprost (0.005%) was replaced by Latanoprost (0.005%)/Timolol (0.5%) FC, Travoprost was replaced by 0.004% Travorost/0.5% Timolol FC & Bimatoprost 0.03% was replaced by 0.03% Bimatoprost/0.5% Timolol FC. In all participants only one eye was included in the study when the combination drop or Ripasudil was administered in both eyes. The eye with highest IOP at baseline was selected for study evaluation. If both the eyes had same IOP at baseline then the right eye was selected for evaluation.

At the baseline visual acuity of all patients were tested to rule out best corrected visual acuity worse than 0.6log MAR. Autoperimetry (24-2) was done to rule out the advanced case of glaucoma at baseline. It was also used as a safety assessment parameter & performed at baseline & at the end of the study at 3 months. Slit lamp biomicroscopy was done to assess the safety & side effects in all visits. Undilated fundoscopy was done during all follow up visits to rule out any fundus changes during the study. Goldman applanation tonometry was done in each visit by single observer to rule out observer dependant changes and at a definite time in the OPD (10 am to 12 pm) in all patients to avoid any diurnal variations. Gonioscopy was performed at the screening visit in all participants to rule out angle closure disease. All participants had their BP& pulse rate measured at each visit.

The number of adverse events & safety were examined & compared between the treatment groups at baseline, 3 weeks, 6 weeks & after 3 months of the study.

Statistical analysis :

ANOVA test was done to check the value of the data at baseline to find out any significant difference between the 2 groups. The IOP, BP & pulse rate were compared within groups by use of paired T- test & between the 2 groups by unpaired T test. The IOP reduction width & rate were compared between baseline & at 3 weeks, 6 weeks & 3 months after starting of treatment. Adverse drug reactions were examined & compared between 2 groups. P value lower than 0.05 were statistically significant.

Results

A total of 18 patients in the switched group & 18 patients added group were recruited in this study but there was 1 drop out in the added group, so total 18 & 17 patients were analysed in the switched group & added group respectively.

No significant difference was found between the two groups in age, male female ratio, number of pre-treatment medication & prostaglandin administration period, IOP, visual field mean deviation (decibel), systolic BP, diastolic BP, pulse rate at the baseline (Table 1, Fig 1).

In the switched group mean IOP after 3 months was 17.3±2.73 mm hg & 16.88±3.01mm hg in the added group, both of which were statistically significantly lower than baseline (switched group 19.55±3 mm hg & added group 19.29 ±3.13 mm hg). Mean IOP change noted after 3 months was 2.22±0.85 in the switched group & 2.41±0.77 in the added group & percentage change rate of IOP was 11.38±4.04 in the switched group & 12.63±4.22 which are statistically significant ($p<0.001$) but there was no statistically significant difference between the 2 groups in mean change of IOP & percentage change rate (Table 2, Fig 2).

At the end of 3 months study there was no significant change of systolic BP, diastolic BP & pulse rate in both the switched group & study groups, and the inter group difference was also not significant.

Table 1 — *Participants demographics & ocular characteristics*

Patient characteristics		Switched group	Added group	P value
Number		18	17	-
Sex ratio (M : F)		10 : 8	8 : 9	-
Age (Years)		61.22±7.62	64.65±9.12	0.25
Pretreatment medication	Latanoprost	4	3	-
	Travoprost	5	6	-
	Bimatoprost	9	8	-
Mean PG treatment period (months)		6.61±1.89	8.2±172	0.001
Mean IOP (mm Hg)		19.56±3.0	19.29±3.14	0.81
Visual field (Mean; MD, dB)		6.76±1.93	7.19±1.91	0.52
Mean Systolic BP (mm Hg)		127.56±9.27	127.18±9.68	0.91
Mean Diastolic BP (mm Hg)		79.67±3.54	77.18±4.66	0.92
Mean Pulse rate		79.11±6.05	75.41±5.30	0.07

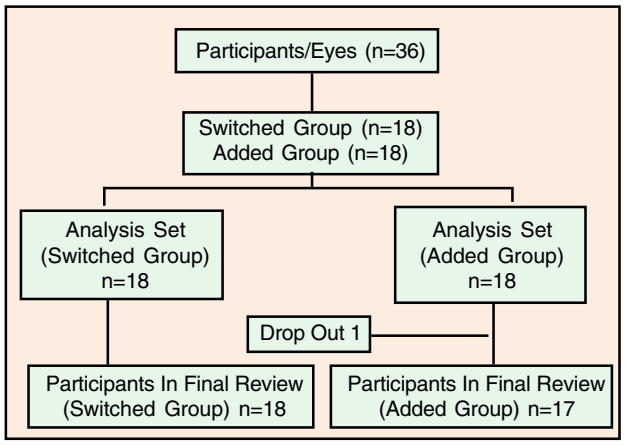


Fig 1 — Showing patient recruitment and randomisation

Systemic adverse events like palpitation, drowsiness, alteration of taste etc were also not statistically significant in our study participants in this interval. None of the study groups had any serious systemic side effects in our study (Table 3).

In the safety analysis total 4 patients had adverse reactions in switched group and 6 patients had adverse drug reactions in added group which was not statistically significant. Conjunctival hyperaemia was the commonest side effect in added group which was 23.53% which developed early after instillation of Ripasudil & resolved within few hours. However, in either of the groups, there was no discontinuation of treatment drugs due to any serious side effect (Table 4).

Discussion

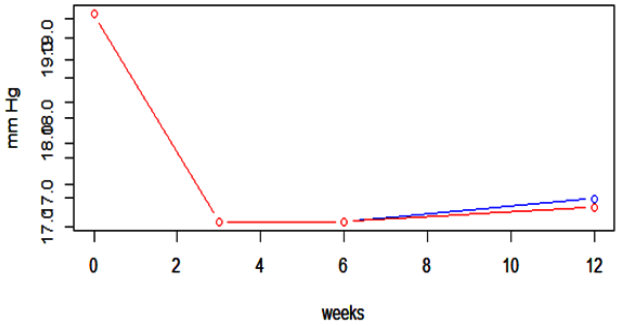
Ripasudil was first approved in Japan in 2014 for the treatment of glaucoma. There are many studies involving Japanese population showing efficacy of Ripasudil in various subtypes of glaucoma patients. Use of Ripasudil as adjunct may act via different mechanisms resulting in sufficient reduction of IOP without competition with other medicines. According to literature, it is the first drug to directly target the conventional outflow pathway. In the early phase (within few hours of instillation) it widens the trabecular meshwork by deforming the cytoskeleton of trabecular cells & loosening the intracellular junction within the schlemm's canal endothelium & in the late phase (within a few months of instillation) the extracellular matrix may reform , leading to reductions in tissue resistance[7,14].

Previously a 2 months study involving Japanese patients with POAG demonstrated that adjunctive treatment with Ripasudil resulted in significant reduction of IOP at the time of peak efficacy. Studies have reported positive effects from the use of Ripasudil combined with Latanoprost for treatment of POAG.

A one-year study on patients with POAG, ocular hypertension & pseudo exfoliation glaucoma in Japan revealed IOP reduction at the time of peak efficacy

Table 2 — *Efficacy evaluation – mean IOP reduction & change rate*

	Switched group	Added group	T test
Mean IOP change at 3 months(mm Hg)	2.22±0.85	2.41±0.77	P=0.25
Change rate%	11.38±4.04	12.63±4.22	P=0.19



Graph showing mean IOP (mm of Hg) of switched group & added group of patients from baseline to end of study (12 weeks)
[Blue : switched group mean IOP; Red: added group mean IOP]

Fig 2 — Combined plot of IOP change of 2 groups

Table 4 — *Adverse drug reactions*

Adverse reaction	Switched group	Added group	P value
Total no of ADR	4 (22.22%)	6 (35.29%)	0.19
Conj. hyperaemia	1 (5.56%)	4 (23.53%)	0.06
Blepharitis	-	1 (5.88%)	0.15
Allergic conjunctivitis	-	-	
Eye irritation	2 (11.11%)	1 (5.88%)	0.55
Eyelid pruritus	-	-	
SPK	-	-	
Palpitation	1 (5.56%)	-	0.16
Others	-	-	

was 3.7 mm Hg in patients with Ripasudil monotherapy & 1.7 to 3 mm Hg in patients having adjunctive therapy with PG & beta blocker[8].

Table 3 — *Blood pressure & pulse rate chart of the study groups*

Variables (Mean)		Baseline	After 3weeks	After 6weeks	After 3 months	P value
Systolic BP (mm Hg)	Switched group	127.56±9.27	128.89±6.97	130±8.11	127.78±10.48	P=0.07
	Added group	127.18±9.68	128.24±8.08	127.53±8.3	126.82±11.29	P=0.42
Diastolic BP (mm Hg)	Switched group	79.67±3.54	79.78±3.39	78.67±4.67	77.78±4.76	P=0.09
	Added group	77.18±4.66	77.76±4.66	76.35±6.07	78±6.25	P=0.21
Pulse rate (Bpm)	Switched group	79.11±6.05	80.06±4.22	77.56±5.23	77.44±5.23	P=0.13
	Added group	75.41±5.30	75.64±5.20	75.88±6.56	75.76±6.01	P=0.39

Three previous studies indicated Ripasudil had a significant IOP lowering effect even for POAG patients who were already undergoing maximal drug treatment[9,13].

When patients were divided in groups with respect to the time of IOP measurement, greater IOP reduction was observed in morning visit group nearly 1.9mm of Hg & no significant reduction in afternoon visit group. According to studies, IOP lowering effect of Ripasudil reaches peak level 2 hours after administration & then decreases to near trough level by 12 hour after administration[14]. This suggests chances of underestimation of efficacy of Ripasudil in clinical practice depending on time of IOP measurement relative to administration.

A previous study showed that 55.9% of the participants experienced conjunctival hyperaemia after initiating Ripasudil use, with other adverse reactions including ocular irritation, superficial punctate keratitis and nasopharyngitis[15].

In our study we measured IOP at a definite time of the day in each visit. Further studies should consider the measurement time relative to Ripasudil instillation for more appropriate evaluation of the efficacy. Our study group was small & only POAG patients were studied for 3 months duration & it is necessary to evaluate the IOP lowering effect of Ripasudil in long term, involving large number of patient of various glaucoma subtypes.

Ripasudil is showing a promising result as a new weapon in our glaucoma armamentarium & can be used effectively even in patients with systemic illness (eg, cardiac illness, asthma) as well as ocular comorbidities (eg, decompensated cornea, diabetic macular edema, uveitis etc) where other glaucoma medications are contraindicated.

Conclusion

From this study it can be concluded that switching from prostaglandin monotherapy to PG/Timolol fixed combination or adding Ripasudil therapy to prostaglandin are both equally safe & effective in control of IOP in short term in POAG patients with insufficient IOP control with prostaglandin monotherapy.

References

1 Quigley HA, Broman AT — The number of people with glaucoma worldwide in 2010 & 2020. *Br J Ophthalmol* 2006; **90:** 262-7

2 Heijl A, Leske MC, Bengstsson B, Hyman L — Reduction of intraocular pressure & glaucoma progression ; Results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol* 2002; **120:** 1268-79.

3 Francis BA, Alvarado J — The cellular basis of aqueous outflow regulation. Curr. Opin. *Ophthalmology* 1997; **8:** 19-27

4 Schmier JK, Hulme-Lowe CK, Covert DW — Adjunctive therapy patterns in glaucoma patients using prostaglandin analogs. *Clin Ophthalmol* 2014; **8:** 1097-104.

5 Robin AL, Lee K, Wogen J — Frequency of adjunctive medication use associated with bimatoprost, travoprost& latanoprost therapy. Presented at the American glaucoma society of general meeting, San Francisco 2003, scientific poster #12

6 Rao PV, Deng PF, Kumar J, Epstein DL — Modulation of aqueous humor outflow facility by the Rho -kinase inhibitor Y- 27632. *Invest Ophthalmol Vis Sci* 2001; **42:** 1029-37.

7 Inoue T, Tanihara H — Rho- a- 12.ssociated kinase inhibitors: A novel glaucoma therapy. *Prog Retin Eye Res* 2013; **37:** 1.

8 Tanihara H, Inoue T, Yamamoto T, Kuwayama Y, Abe H, Araie M, *et al* — Phase 2 randomized clinical study of a Rho kinase inhibitor, K -115 in primary open-angle glaucoma and ocular hypertension. *Am J Ophthalmol* 2013; **156:** 731-6.

9 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 combined with Timolol or Latanoprost :areport of 2 randomized clinical trials, *JAMA Ophthalmol* 2015; **133(7):** 755-61.

10 Tanihara H, Kakuda T, Sano T — Safety & efficacy of ripasudil in Japanese patients with glaucoma or ocular hypertension: 3 months interim analysis of ROCK-J, a post- marketing surveillance study. *Adv Ther* 2019; **36(2):** 333-43.

11 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.

12 Inoue K, Ishida K, Tomita G — Effectiveness and safety of switching from prostaglandin analog monotherapy to prostaglandin/timolol fixed combination therapy or adding ripasudil. *Jpn J Ophthalmol* 2018; **62(4):** 508-16.

13 Inazaki H, Kobayashi S, Anzai Y — one year efficacy of adjunctive use of Ripasudil, a rho- kinase inhibitor, in patients with glaucoma inadequately controlled with maximum medical therapy. *Graefes Arch Clin Exp Ophthamol* 2017; **255(10):** 2009-15.

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 Terao E, Nakakura S, Fujisawa Y, Fujio Y, Matsuya K, Kobayashi Y, *et al* — Time course of conjunctival hyperemia induced by a Rhokinase inhibitor anti-glaucoma eye drop: Ripasudil 0.4. *Curr Eye Res* 2017; **42:** 738-42.