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Do Ripasudil or Travoprost Provide Any Quantitative Nerve Fibre Layer Protection along with Decrease in Intraocular Pressure? A Comparative Short-Term Study in Primary Open Angle Glaucoma

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Abstract: ***Purpose: To evaluate the effect of ripasudil versustravoprost on intraocular pressure and retinal nerve fibre layer in patients suffering from primary open angle glaucoma (POAG). Design: A single center, prospective, interventional, parallel group, hospital based randomized comparative study. Method: Fourty eyes of fourty patients suffering from POAG were medically treated with ripasudil or travoprost by randomizing them into 2 groups for a period of 6 months and studying their effects on intraocular pressure and retinal nerve fibre layer. Results: A total of 40 patients were enrolled, 20 randomized to ripasudil groupand 20 randomised to travoprost group. The mean age being 53.00±16.94 years in ripasudil group and 52.15±15.97 years (p value 0.871). The baseline intraocular pressures for ripasudil and travoprost from their baseline of 23.50±2.04 mmHg and 23.95±2.24 mmHg dropped to 19.00±2.45 mmHg and 16.95±2.44 mmHg on their last visit respectively (p value < 0.001). The baseline retinal nerve fibre thickness for ripasudil group was 117.40±12.19 microns and on last follow up at 6 months was 112.85±14.08 microns, with a change of 4.55±4.36 microns (p value <0.001). The baseline retinal nerve fibre thickness for travoprost group was 115.25±11.44 microns and on last follow up at 6 months was 111.10±13.29 microns, with a change of 4.15±4.32 microns (p value <0.001). Conclusion: Travoprost showed greater intraocular pressure lowering effect than ripasudil. And ripasudil and travoprost showedno statistically significant retinal nerve fibre layer protective effects in our study.***

Keywords: Ripasudil, travoprost, primary open angle glaucoma, intraocular pressure, retinal nerve fibre layer

1. Introduction

Glaucoma is the most important cause of irreversible vision loss globally.[1] According to prevalence studies, 79.6 million people may have glaucoma in 2021.[2]Despite of aggressive treatment measures there seems to be no single drug or agent that can halt or treat glaucoma. Hence newer drugs need to be researched and compared.

Travoprostis a prostaglandin analogand was introduced 2001. Increasing uveoscleral outflow is the principal mechanism of lowering intraocular pressure.[3]

Ripasudil was approved for treating glaucoma and ocular hypertension in 2014.[4,5] It is a Rho-kinase inhibitor that acts via the G – protein pathway.[6,7]

2. Methods

The study was started after approval by institutional ethical committee. All ethical standards were maintained under the tenets of the Helsinki Declaration of 1964, as revised in 2013.

The study was a single-centre, prospective, comparative, randomized, and parallel-group study. Candidate patients for the study received complete information regarding the protocol and written informed consent was obtained from each participant before entry into the study. Randomization was done by the random chit method.

All subjects underwent complete ophthalmic examination. Patients were examined using slit-lamp examination, IOP (Goldmann applanation tonometry): All measurements were taken at each time point at least twice by well-trained specialists. If the measurements differed by 2 mmHg, a third measurement was taken. The mean of 2 or the median of 3 recordings was used for analysis, gonioscopy examinations, and visual acuity testing with refraction, pachymetry, indirect ophthalmoscopy, and retinal nerve fiber layer optical coherence tomography was done for each patient.

If patients were previously on some other intraocular pressure-lowering medications, an appropriate washout period (prostaglandin analogs and b-blockers, 4 weeks or more; other IOP-lowering medications, 2 weeks or more) was ensured. Each medication was to be instilled daily at a specific time each day, and no other IOP-reducing therapy was permitted. Compliance of the drugs was ensured.

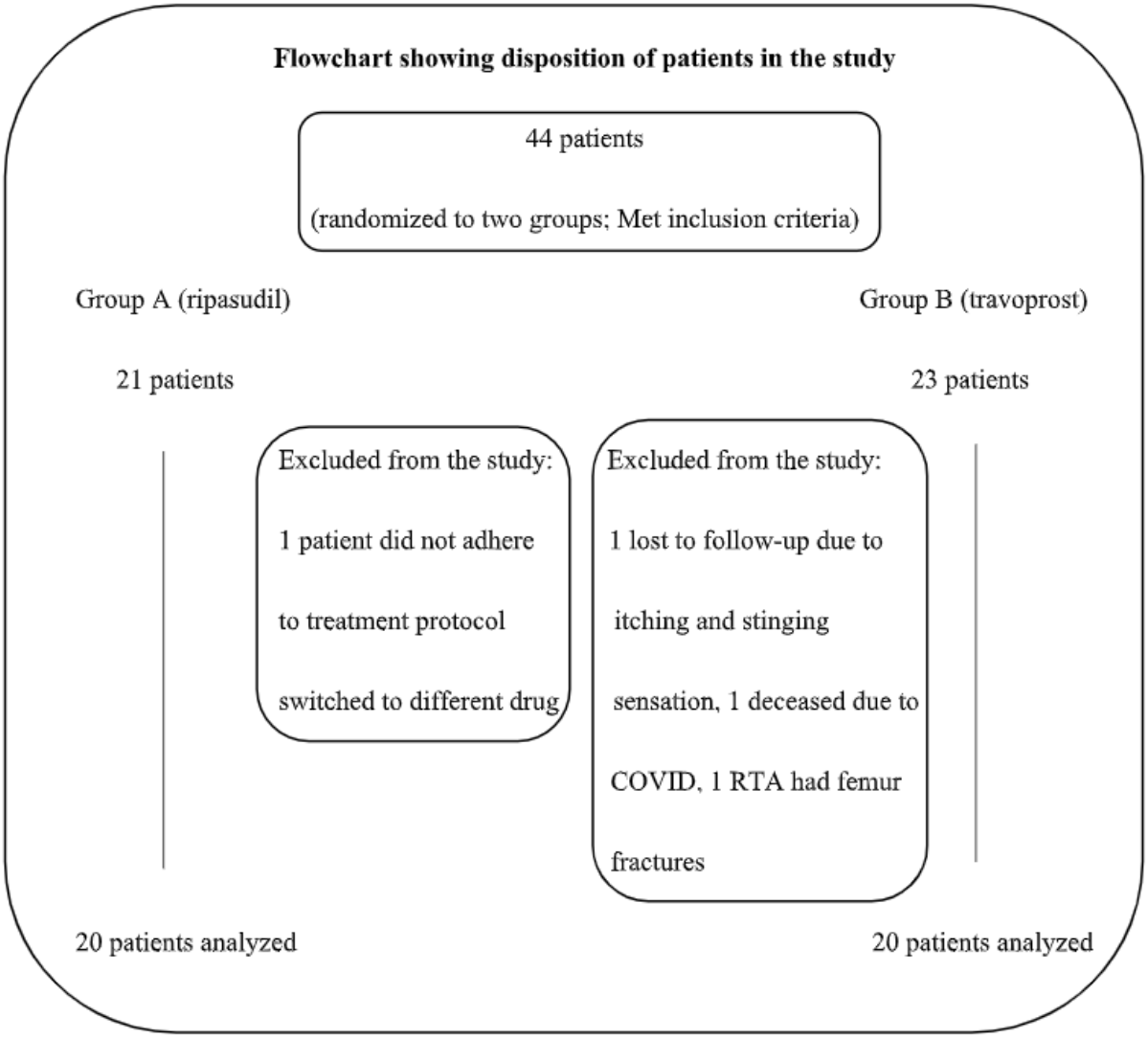
Inclusion criteria: Patients suffering from primary open angle glaucoma, patients who will give written informed consent.

Exclusion criteria: Patients who chose to opt out of research/ do not give consent for the study, angle-closure glaucoma or with narrow angles defined as grade 2 or less of the Shaffer classification by gonioscopy, secondary causes of elevated IOP, patients with IOP levels of 30 mmHg or higher, use of any glucocorticoid or ocular nonsteroidal anti-inflammatory agents, which inhibit cyclooxygenase and prostaglandin synthesis, corneal abnormalities preventing reliable IOP measurement, previous filtration surgery, life-threatening or debilitating disease, having a single eye, pregnancy.

Follow up: The follow up was conducted on monthly basis after a baseline evaluation. On every follow up the patients were assessed for vision, intraocular pressure and central corneal thickness. On the first and the last visit the patients were evaluated for retinal nerve fibre layer optical coherence tomography.

This study was conducted among 40 patients randomly divided equally into two groups: 20 patients were randomized to the group A (ripasudil 0.4% w/v) and the other 20 to the group B (travoprost 0.004% w/v). Patients had to instill the eyedrops in a once-a-day regimen at 8 p.m. every day. Statistical analysis was done using t-test. The following observations were recorded in the study.

3. Results



Mean age in group A was 53 ± 16.94 years and in group B was 52.15 ± 15.97 years. Statistically there was no difference (p=0.87) between the two groups.

In group A there were 75% males and 25% females whereas in group B there were 65% males and 35% females. Statistically there was no difference between the two groups (p=0.73).

Individually the effects of the drugs of the intraocular pressure and retinal nerve fiber layer have been mentioned as follows:

It can be clearly seen that in the group treated with ripasudil eye drops had a mean baseline IOP of 23.50 ± 2.04 (mean ± SD) mmHg and after treatment the IOP reduced by 3.10 ± 1.97 (13% decrease from baseline),4.70 ± 1.84 (20% decrease from baseline), 4.05 ± 2.09 (17% decrease from baseline), 4.85 ±1.42 (20.6% decrease from baseline), 4.30 ± 1.42 (18.2% decrease from baseline), 4.50 ± 1.85 (19.1% decrease from baseline) (mean ± SD) mmHg at first follow up, second follow up, third follow up, fourth follow up, fifth follow up, sixth follow up respectively. And the drug in relation to IOP lowering effect has high statistical significance (p=0.00) at all follow up points.

It can also be seen that in the group treated with travoprost eyedrops had a mean baseline IOP of 23.95 ± 2.23 (mean ± SD) mmHg and after treatment the IOP reduced by 3.75 ± 2.57 (15.6% decrease from baseline),5.45 ± 1.90 (22.7% decrease from baseline), 6 ± 2.42 (25% decrease from baseline), 5.90 ± 1.86 (24.6% decrease from baseline), 7.45 ± 2.23 (31.1% decrease from baseline), 7 ± 2.05

(29.2% decrease from baseline) (mean ± SD) mmHg at first follow up, second follow up, third follow up, fourth follow up, fifth follow up, sixth follow up respectively. It is seen that this drug too is statistically significant in terms of IOP lowering effect (p=0.00) in every follow up.

Table 1: Comparing intraocular lowering effect (Group A and Group B)

	Group A		Group B		Result (P value)
	Mean	SD	Mean	SD	
BASELINE	23.50	2.04	23.95	2.24	0.509 (NS)
FIRST FOLLOW UP	20.40	2.95	20.20	2.93	0.830 (NS)
SECOND FOLLOW UP	18.80	2.59	18.50	2.74	0.723 (NS)
THIRD FOLLOW UP	19.45	2.37	17.95	2.24	0.046 (S)
FOURTH FOLLOW UP	18.65	2.43	18.05	2.31	0.428 (NS)
FIFTH FOLLOW UP	19.20	1.96	16.50	2.06	0.0001 (S)
LAST FOLLOW UP	19.00	2.45	16.95	2.44	0.011 (S)

S = Significant; NS = Non-Significant; the follow ups were taken monthly till six months after a baseline follow up

It can be seen from the above table that when comparing the two drugs head-to-head on the effects of intraocular pressure lowering effect. In the beginning the two drugs didn't show any statistical significance but as follow ups progress the mean difference between the two drugs widens and becomes statistically significant, where the drug in group B (travoprost) achieves a lower reduction in IOP.

Table 2: Comparing RNFL changes between Group A and Group B

		Group A	Group B
RNFL (Mean ± SD)	Baseline	117.40 ± 12.19	115.25 ± 11.44
	Last follow up	112.85 ± 14.08	111.10 ± 13.29
	Change	4.55 ± 4.36	4.15 ± 4.32
	p value	<0.001 (NS)	<0.001 (NS)

S = Significant; NS = Non Significant; for RNFL the patients were assessed on the first visit and on the last visit that is on the sixth month.
It can be seen that ripasudil group patients had a change from a baseline RNFL of 117.40 ±12.19 (Mean ± SD) micron to 112.85 ± 14.08 microns in thickness and the travoprost group patients changed from a baseline RNFL value of 115.25 ± 11.44 to 111.10 ± 13.29 microns in thickness. Which statistically when calculated comes to be significant (p=0.00).

4. Discussion

The treatment of glaucoma has come a long way from the introduction of pilocarpine as the first drug for the treatment of glaucoma to prostaglandins that are the preferred choice of treatment for many doctors. But even after so much research and advancements we still need to assess and evaluate other alternatives for halting the progression or even reversing the damage caused by glaucoma.

Our two groups had a mean age of 53 ± 16.94 years for group A and 52.15 ± 15.97 years for group B which showed no statistical difference between the two groups (p=0.87). Also, the gender distribution was more weighted towards the male sex in both the groups.

Ripasudil in our study caused a 3.10 mmHg (13%) to 4.85 (20.6%) mmHg decrease in IOP, these results are not only significant in themselves but also show agreement with other studies. Tanihara et al in their 52 weeks long term study of ripasudil led to a reduction in IOP of 2.6 mmHg (13.5%) at the trough and 3.7 mmHg (19.4%) at the peak when given as monotherapy.[8]In another post-marketing surveillance study Tanihara et al enrolled a total of 3058 patients and noted a significant IOP decrease in patients having POAG (- 2.9±4.2 mmHg) which correlates well with the IOP decrease of the range of 3.10 to 4.85 mmHg in our study.[9]Fukakuchi et al in a multicentric cohort study found that the mean overall IOP reductions from baseline at 1, 3, and 6 months were −19.4±25.1%, −20.0±27.1%, and −23.4±25.6% respectively.[10] Comparing this to our study we got a similar decrease in IOP of about 20.6% from the baseline.

Now coming to the travoprost group, which in our study achieved an IOP reduction within a range of about 15.6% to 31.1% of the baseline. Similarly, Goldberg et al in their study had a mean baseline IOP among all subjects of approximately 26 mmHg and a mean IOP reduction ranging from 8.0 to 8.9 mmHg with travoprost 0.004% which is about 30% which correlates well with our study.[11] Netland et al in their 12 months study had a mean IOP of approximately 25–26 mmHg in untreated patients. After the study period, the mean IOP ranged between 17.7 to 19.1 mmHg with travoprost 0.004%.[12] In our study, the untreated mean was 23.95 and the IOP decrease ranged between 16.50 to 20.20 mmHg the percentage decrease in the two studies was similar (around 30 percent).

The other important thing to note is the IOP reduction caused by the drugs ripasudil and travoprost among themselves. Comparing these drugs, we see a visible difference between the IOP lowering potential where travoprost at 31.1% IOP reduction seemingly looking the more potent drug over ripasudil at 20.6% decrease in IOP. Thus, proving travoprost-like drugs as the drug of first choice for many.

In our study both drugs showed statistically significant (p=0.00) decrease in retinal nerve fibre layer values pointing to the fact that none of the drugs showed any protection to retinal nerve fiber damage during the time duration of the study. There have been studies supporting the neuroprotective role of ripasudil wherein ripasudil according to these studies is being considered as a novel drug for neuroprotection in glaucoma.[13] On the contrary,

our study with quantitative data disproves the above considerations also there is no particular study (or no study in our knowledge) that takes retinal nerve fiber layer as a variable and provides us with quantitative data. On a more modest approach, it might also be the case that the small sample size in our study might not make the neuroprotective effect that evident making the importance of a larger study felt.

In our study, only hyperemia was seen as the adverse effect seen in the ripasudil group which was reported by 4 patients. It needs to be noted that the hyperemia in our patients lasted for only about an hour or two and resolved on its own. Furthermore, it is possible that the conjunctival hyperemia was transient and disappeared in the time between application and examination leading to a possibility of underestimating the cases of hyperemia. Also, in the travoprost group 2 patients had hyperemia and 1 patient had itching and burning sensation who was lost to follow up. It was also worth noting that the adverse effects such as eyelash growth, iris hyperpigmentation noted in other studies were not seen in our study.[14]

The drawbacks of the study were the number of patients in the study, follow up that could have been longer, not screening for racial differences, evaluation for placebo effect was not done and finally, we did not compare the IOP lowering effects of the drugs in fixed-dose combinations.

5. Summary

The study underlines the fact that travoprost produces greater intraocular lowering of pressure than ripasudil and also provides us with quantitative data which shows that both these drugs have no retinal nerve fibre protective action for six months follow up in this study.

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Conflict of interest: Nil

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