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TO ASSESS NEUROPROTECTIVE ROLE OF RIPASUDIL IN MILD TO MODERATE CASES OF PRIMARY OPEN ANGLE GLAUCOMA

Ophthalomology

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KEYWORDS

INTRODUCTION

Glaucoma is a family of multifactorial optic neuropathies characterized by loss of retinal ganglion cells (RGCs) leading to typical optic nerve head (ONH) damage characterized by classical optic disc cupping and distinctive visual field defects. It is the leading cause of irreversible blindness and was estimated to affect 80 million people worldwide by the end of 2020.[1] Although the pathogenesis of the disease is unknown, it is well established that the main risk factor for glaucoma is elevated Intraocular Pressure (IOP).[2]

Since ages, the primary target for slowing down the progression of disease is to control the IOP, but despite this in few patients the damage keeps on progressing. Present : IOP lowering by: [3]

1) Decreasing the production of AH (beta blockers, CAI, alpha agonist)
2) Improving AH outflow through unconventional pathway (uveoscleral)

Need :

drug that specifically treat the diseased TM/ Schlemms's canal complex is the need. Cells in the pathway could not appropriately change their shape to decrease resistance to aqueous outflow and reduce IOP. In this regard Rho-associated kinase inhibitors (ROCK) considered as a potential class of oculo hypotensive drug.

Ripasudil is a derivative of fasudil, ROCK inhibitor used for treatment of glaucoma and ocular hypertension.

ROCK inhibitor: MOA : [4]

1. Relax TM through inhibition of actin cytoskeleton contractile tone of smooth muscle
2. ROCK inhibitors induces extracellular matrix re organization and widens the empty spaces in TM
3. They also weakens cell attachment to its extracellular matrix which results in relaxation of the whole of TM tissue and hence wider empty spaces

Neuroprotection :

All patients do not get benefit from an IOP lowering therapy only. RGC death is very common feature of all types of glaucoma. Axons are limited in their ability to regenerate when injured due in part to the presence of growth inhibitors [5]

The need :

new therapeutic strategies should focus on preventing or retarding RGC death, but also on sufficient and lengthy repair/regrowth of damaged RGC axons in the optic nerve. Rho kinase inhibitors prevent axonal degeneration and promote axonal regeneration.

METHODS:

This is a hospital based prospective cohort study

2.1 Patients:

Two cohorts of individual attending Glaucoma Clinic of Department of Ophthalmology, GSVM Medical College & LLR Hospital, Kanpur, Uttar Pradesh were recruited, Group A (n=22) consisting of POAG or ocular hypertensive patients receiving Ripasudil and Latanoprost, Group B (n=22) consisting of POAG or ocular hypertensive patients receiving Latanprost and Timolol eyedrops. POAG were identified as patients with open anterior chamber angle, glaucomatous optic nerve head changes, visual field defect and an IOP of more than Or equal to 21mm Hg on atleast two occasions. OHT were identified as patients with open anterior chamber angle, normal disc, normal visual fields and IOP of more than Or equal to 21 mmHg on atleast two occasions.

Better eye per patient were selected. Patients of angle closure glaucoma, congenital glaucoma, secondary glaucoma, with history of any ocular trauma or eye surgery, with cardiovascular disorder or with any neurological disorder were excluded.

The study was approved by the ethical review committee (Institutional Review Board) of our own institution; Ref. No: EC/BMHR/2020/44, Dated: 22-11-2022; and was conducted in accordance with Good Clinical Practice within the tenets of the Helsinki's agreement. Each patient/subject was required to sign an informed consent statement before being enrolled into the study and prior to any study measurements being taken.

2.2 History And Examination

The patients were subjected to detailed history and comprehensive examination.

UCVA and BCVA were taken using Snellen's chart. Detailed slit lamp examination was done and angle of the anterior chamber was assessed by gonioscopy done using Goldmann 3 mirror goniolens. Fundua examination was done by +90D to observe any ONH changes. IOP was measures using Applanation tonometer.

OBF parameters were recorded via 13.5-MHz probe with a pulsed Doppler device. Subject was made to lie in the supine position with the head in a neutral position and both eyes closed and in primary gaze position. After application of coupling gel, the transducer was softly placed over the upper eyelid in an axial plane. This sonographic section provides a transverse view of the globe and the structures of the retrobulbar area. In the imaged area, red colour denotes flow towards the probe and blue colour away from the probe. Three retrobulbar arteries, namely, Central retinal artery(CRA), Ophthalmic artery(OA), and Short posterior ciliary artery(SPCA) were identified by their pulsations and ocular blood flow parameters, Peak Systolic Velocity(PSV), End Diastolic Velocity(EDV) and Resistivity Index(RI) thus recorded.

Visual fields as predictor of glaucomatous damage were assessed by Humphrey's field analyser.

2.3 Statistical Analysis:

Data was collected and entered in Excel Spreadsheet for statistical analysis. GraphPad InStat software was used for applying tests of

significance. Paired t test was used to compare between two variables within the group. Unpaired t test was used to compare between variables between the groups. Anova test was applied to compare between >2 groups. P value <0.05 is considered significant.

3.RESULTS:

A total of 42 patients were enrolled in the study divided into two groups:
Group 1: Patients of POAG or ocular hypertension receiving Ripasudil and Latanoprost eyedrops
Group 2: Patients of POAG Or ocular hypertension receiving Latanoprost and Timolol eyedrops

Table 1 enlist the demographic data and table 2 summarizes average baseline parameters of the subjects.

Table 3,4,5,6 depict the changes in the baseline parameters in IOP, PSV, EDV, RI of OA in Group 1 and Group 2.

In our study we found out that mean IOP was significantly lowered (p<0.00001) by both the groups but mean IOP lowered by Group 1 was more than Group 2. (p <0.0001)

In our study we found out that mean PSV, EDV OA was significantly (p<0.00001) raised & there was significant fall(p<0.00001) in RI value after 1month and 3month of treatment in GROUP1 suggesting increased ocular blood flow.

Table 1: Demographic Data:

AGE GROUP	GROUP 1	PERCENTAGE	GROUP 2	PERCENTAGE
41-50	11	52.38%	12	57.14%
51-60	9	42.85%	9	42.85%
>60	1	4.76%	0	0%

Table 2: Baseline Charecterstics:

	GROUP 1	GROUP 2
AGE GROUP		
41-50 51-60 >60	11 9 1	12 9 0
SEX		
MALE FEMALE	11 10	12 9
PARAMETERS	Mean SD	Mean SD
Vision (log mar)	0.60 ± 0.31	0.70 ± 0.33
IOP (mmHg)	30.04 ± 3.52	31.04 ± 3.73
Visual field (MD)	8.65±5.92	8.62±5.97
PSV (cm/s) [OA]	30.04±6.07	32.83±5.09
EDV (cm/s) [OA]	4.81±1.53	4.90±0.83
RI	0.82±0.033	0.84±0.004
Endothelial count	2992±5.42	3012±7.6o0

Table 3: Changes In Iop:

	Resting (mmHg)	After 15 days (mmHg)	After 1 month (mmHg)	After 3month (mmHg)
GROUP 1	30.04±3.52	24.00±2.48	19.66±2.98	16.85±2.00
GROUP 2	31.14±3.73	28.09±2.94	25.52±3.47	23.00±1.44

Table 4: Changes In Psv (cm/s) Oa

	INITIAL	1MONTH	3MONTH
GROUP 1	30.04±6.07	35.55±2.67	39.34±1.32
GROUP 2	32.83±5.09	32.77±4.95	32.83±4.95

Table 5: Changes In Edv (cm/s) :

	INITIAL	1MONTH	3MONTH
GROUP 1	4.81±1.53	6.13±1.20	7.38±0.66
GROUP 2	4.9±0.83	4.91±0.72	5±0.69

Table 6: Changes In Ri:

	INITIAL	1MONTH	3MONTH
GROUP 1	0.82±0.033	0.80±0.027	0.78±0.024
GROUP 2	0.84±0.004	0.84±0.009	0.83±0.008

4. CONCLUSION:

- Ripasudil has improved ocular blood flow in Group 1 which might indicate that it has neuroprotective role in mild to moderate cases of POAG.
- Ripasudil has pressure lowering effect in mild to moderate cases of POAG
- Pressure lowering effect of Ripasudil + Latanoprost is more than Timolol+ Latanoprost

5. DISCUSSION:

In our study we found out that Ripasudil has pressure lowering effect in mild to moderate cases of POAG and pressure lowering effect of Ripasudil+Latanoprost was more than Timolol and Latanoprost.

Our study correlated with **Yoshio Kaneko** et al.[6] which was done to see Additive Intraocular Pressure-Lowering Effects of Ripasudil with Glaucoma Therapeutic Agents in Rabbits and Monkeys it was found that maximum IOP-lowering effect or prolongation of IOP-lowering effect in combined regimens with β-blocker, αβ-blocker, α2-agonist, CAI, PG analog, and fixed combination of these agents. The mechanisms of action are due to increment of conventional outflow by ripasudil treatment.

Study done by **Hidenobu Tanihara** et al. JAMA Ophthalmol. 2015 Jul[7] stated that additive IOP-lowering effects of ripasudil from placebo at trough and peak levels in combination with timolol and at peak level in combination with latanoprost.

In our study we concluded that OBF parameters PSV, EDV significantly increased (p<0.00001) & RI (p<0.00001) decreased in patients receiving Ripasudil+Latanoprost . Our study correlated with **Odunlami Olufemi Adeyinka** et al [8] who suggested the increase in IOP in the POAG group was statistically significantly negatively correlated with PSV and EDV and positively correlated with RI for both OA and CRA and **Cengiz Akarsu** et al.[9] who suggested that Glaucoma patients had lower end-diastolic velocities and higher resistivity indices than did normal subjects in the ophthalmic (P=0.003 and P=0.003, respectively), posterior ciliary (P=0.001 and P<0.001, respectively), and central retinal arteries (P=0.03 and P=0.04, respectively). Glaucoma patients had significantly lower end-diastolic velocity and higher resistivity index than did patients with ocular hypertension in the posterior ciliary artery (P=0.04 and P=0.001, respectively). **Yasushi Wada** et al[10] concluded that Topical instillation of ripasudil increased blood flow around the ONH in the eyes of normal rats.

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