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Comparison of Efficacy and Safety of Ripasudil 0.4% and Bimatoprost 0.01% in Patients of Primary Open Angle Glaucoma and Ocular Hypertension

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Abstract:

Objective: To compare Mean Intraocular pressure reduction produced POAG and OHT patients, classified according to their baseline Intraocular pressure (Group A with baseline Intraocular pressure between 22-25mmHg, Group B with baseline Intraocular pressure between 26-30mmHg), at last follow-up visit at 3 months.

Study Design and Type: Prospective double blind randomized control trial study.

Methodology: IOP measurement with a Calibrated Goldmann Applanation Tonometer (GAT) was done, with Diurnal variation recording at 8am, 12.00 and 4pm as baseline, and then at 2 weeks, 6 weeks and 3months. Two consecutive measurements of IOP in each eye were obtained at each time point and average of the two was taken as the IOP. If the 2 measurements differ by >2mmHg, a 3rd measurement was obtained and the middle value of the 3 recordings was taken as the IOP. The data analysis and patient examination took place between February 2021 to till February 2022.

Results: Distributions of patients of primary open angle glaucoma and Ocular hypertension into Base line IOP 22-25mmhg (group 1) and Base line IOP 26-30mmhg (group 2). . Total 35 patients were included in this study one was lost to follow up and hence data analysis was done only on 34 patients. Out of 34, total 23 (67.65%) patients were included in group 1 and 11 (32.35%) patients were included in group 2. Values are expressed as mean, median, ±SD, minimum and maximum. Range of age was 42 to 65 years in group 1 and 33 to 64 years in group 2. The mean age was 58.30±6.98 in group 1 and 55.29±8.03 in group 2. The mean IOP at baseline, 2 week, 6 week and 3 months were 23.65±1.43, 16.84±1.95, 14.32±2.54 and 12.23±2.26 in right eye and 23.30±1.66, 16.96±2.2, 14.41±2.48, 12.23±2.23 in let eye in group 1 and 27.09±2.26, 19.88±3.02, 16.91±3.39 and 14.55±3.7 in right eye and 28.18±1.66, 20.48±3.29, 16.91±3.2 and 14.36±3.32 in left eye in group 2, respectively. The mean IOP was significantly more in group 2 as compared to group 1 at baseline to 3 months follow-up in right eye and left eye.

Conclusion: Bimatoprost and Ripasudil drugs significantly reduced the IOP from baseline to 3 months follow up in both lower base line IOP and higher base line IOP group. Bimatoprost was found to be more

effective in decreasing IOP in all patients as compared to Netarsudil especially more in higher base line IOP group.

Keywords: IOP, mean, comparison, groups, Glaucoma, OHT.

Introduction: The chronic, progressive optic neuropathy known as glaucoma causes different morphological changes in the optic nerve head and the layer of retinal nerve fibres. The population of retinal ganglion cells and the visual field have both decreased through time, for which raised IOP is one of the risk factor.[1] IOP is the main modifiable component. Estimated number of glaucoma cases in India at 11.9 million. Glaucoma affects approximately 64.3 million people worldwide (aged 40 to 80), and that figure is predicted to increase to 76.0 million by 2020 and 111.8 million by 2040. Individuals with open-angle glaucoma typically have elevated IOP (normal range: 10–21 mmHg); however, a very small percentage of patients may encounter ocular problems when their IOP is less than 21 mmHg, in which case they are referred to as having normal tension glaucoma. Patients with an IOP > 21 mmHg who do not eventually have visual impairment are referred to as having "ocular hypertension" (OHT) [14]. Controlling the drainage of the eye's aqueous humour is crucial to treating glaucoma. The primary way of escape is conventional outflow, also referred to as trabecular meshwork and Schlemm's canal outflow; uveoscleral outflow, sometimes referred to as unconventional or uveoscleral outflow, makes up a smaller portion of outflow. Topical medications are the first line of defence against IOP, but if they are ineffective, patients may need to switch to laser-based therapy or surgical procedures [14].

In December 2017, the FDA authorised Ripasudil 0.4%, the first medication in a novel family of medications known as Rho kinase (ROCK) inhibitors. This medication can lower episcleral venous pressure and impede norepinephrine transport, in addition to blocking ROCK [17]. It also has other IOP-lowering qualities. The double-blind, randomised, multicenter ROCKET-1 experiment compared the efficacy of Netarsudil 0.02% given once daily at night vs timolol maleate 0.5% given twice daily. The ROCKET-2 research, which had a similar design, added a second Netarsudil 0.02% twice-daily dosing arm. In every study, subjects with OHT or OAG and an IOP between 20 and 27 mmHg underwent a three-month observation period. In both trials, the primary result was a reduction in IOP. Individuals who received timolol in ROCKET-1 demonstrated a 17%-22% drop in IOP compared to patients who received Netarsudil, who showed a 15%-22% reduction in IOP; nonetheless, this was insufficient to demonstrate noninferiority based on pre-set criteria. The primary efficacy population of ROCKET-2, which included patients with an IOP of 25 mmHg, demonstrated mean reductions of 3.3-4.6mmHg and 4.1-5.4 mmHg in patients receiving daily and twice-day Ripasudil, respectively. These drops were comparable to those caused by twice-daily timolol, which caused a drop in blood pressure of 3.7–5.1 mmHg from baseline and demonstrated Ripasudil noninferiority. IOP was lowered by 16%–21% with daily Ripasudil, 22%–24% with twice-day dosage, and 18%–23% with twice-daily timolol [18].

Bimatoprost,a synthetic prostamide, reduces intraocular pressure (IOP) by encouraging aqueous humour evacuation. In patients with open-angle glaucoma or ocular hypertension, long-term treatment (for up to 48 months) with once-daily Bimatoprost 0.03% ophthalmic solution was superior to timolol twice-daily in providing a sustained and consistent reduction in IOP.[19] Bimatoprost 0.03% ophthalmic solution demonstrated efficacy comparable to or greater than that of the prostaglandin analogues latanoprost and travoprost in terms of decreasing IOP and achieving goal IOP levels.

Methodology: The study followed the guidelines contained in the declaration of Helsinki and approval was taken from the institutional Review Board. Informed written consent was taken in each case regarding the purpose of the study and also for publication of data thereafter. It is a Tertiary Eye care hospital based "Interventional randomized parallel group study" This study was conducted from (February 2021 till February 2022).

STUDY POPULATION:
Primary open angle glaucoma and Ocular hypertension

SAMPLE SIZE (N): = $\{(ZA+ZB)^2 \text{ X } A^2\} / D^2$
Zα Is 2.58 For P = 0.01 Zβ Is 1.28 For 90% Power
$= (2.58+1.28)^2 \times (3)^2 / (2)^2$
$= 33.52 = 34$
Total 34 Patients Were Enrolled In Each Group Of Study On The Basis Of Well Define Inclusion And Exclusion Criteria.

STUDY DESIGN:
Prospective double blind randomized control trial study.

INCLUSION CRITERIA:
- All newly diagnosed patient of primary open angle glaucoma and ocular hypertension with IOP between 22-30mmHg were included in the study.
- Eligible patients were screened for inclusion and exclusion criteria and were randomly assigned to each group in a 1:1 ratio.
- 40 years of age or older.
- POAG or OHT in both eyes (POAG in one eye and OHT in the fellow eye is acceptable).

EXCLUSION CRITERIA:
- Patients who are not willing to give a written consent.
- Systemic condition which can increase IOP like sleep apnea syndrome, or decrease IOP like oral beta blockers.
- Patients who are on systemic steroids for any condition like Psoriasis.
- Patients with co-morbidities or those who are psychologically unsound and hence cannot undergo investigations like HFA.
- Variants of POAG like pseudo exfoliation and pigmentary glaucoma.
- POAG patients or ocular hypertensives who have undergone any laser or surgical treatment for glaucoma.
- History of any previous ocular surgery which can affect IOP measurement like (refractive surgery) or clinical assessment of severity of adverse effects like (SICS, RD surgery etc.)
- Patients with history of ocular trauma within past 6 months.
- Any evidence of ocular infection / inflammation like conjunctivitis, blepharitis, iritis etc.
- Any ocular condition which is contraindication for used for any of the two drugs.
- Patients with hazy ocular media.

Patient Work Up:

- Patients willing to participate had the following workup done-
- Informed written consent
- Best corrected visual acuity (BCVA) Snellen visual acuity.
- Patient's age and sex.
- Complete slit lamp examination with documentation of any pre-existing signs and or symptoms at baseline
- IOP measurement with a Calibrated Goldmann Applanation Tonometer (GAT) was done, with Diurnal variation recording at 8am, 12.00 and 4pm as baseline, and then at 2 weeks, 6 weeks and 3months. Two consecutive measurements of IOP in each eye were obtained at each time point and average of the two was taken as the IOP. If the 2 measurements differ by >2mmHg, a 3rd measurement was obtained and the middle value of the 3 recordings was taken as the IOP.
- For randomization into study groups, individuals were required to have an un-medicated IOP between 22 to 30 mmHg at baseline visit. Patients were instructed to in still the medication daily in both eyes at 9 PM. No other ocular medication except preservative free lubricants, were allowed during study period.
  To study the effect of baseline IOP on the IOP lowering efficacy of the two drugs, patients were segregated into two groups, according to their baseline IOP as follows-

Group 1: Base line IOP 22-25mmHg.
Group 2: Base line IOP 26-30mmHg.

Randomization method: As the study groups were formed for IOP lowering efficacy of Bimatoprost and Netarsudil drugs, the randomization was done for Bimatoprost and Netarsudil group. Initially patients were enrolled based on baseline IOP measurements resulting in lower IOP (22-25 mmHg) and higher IOP (26-30 mm Hg) group, consequently each participant of both the groups were given Bimatoprost and Netarsudil on alternate basis resulting in two study group formation at the baseline consisting of 17 patients who were given either Bimatoprost or Netarsudil in each study group (Bimatoprost group and Ripasudil group).
The randomization was done by alternate allocation of both the drugs to the participants in each group of the study without any selection bias.
All patients had undergone a random 1:1 allocation in Netarsudil and Bimatoprost Groups, irrespective of their baseline IOPs.

Analyzing this information gave us an idea about how the IOP decreasing efficacy of Ripasudil 0.4% and Bimatoprost 0.01% is correlated with the baseline IOP.
All patients had undergone Gonioscopy and (CCT) central corneal thickness assessment at baseline visits.
HFA 24-2 and disc photography were done at base line visit.
SS-OCT for RNFL, ONH, GCC

Informed consent: before study the study will be discussed with each subject. Subjects wishing to participate must give written informed consent.
Conflict of Interest: there are no financial conflicts of interest to disclose.

Global clinical score of symptoms: were observed and documented at baseline and then at each follow up visit as follows-

Redness, Burning/ Stinging, Itching, Blurred Vision, Sticky Eye Sensation, Dry Sensation, Foreign Body Sensation, Symptoms Were Recorded as Each Follow Up Visit.

GRADE 0: NONE
GRADE 1: MILD
GRADE 2: MODERATE
GRADE 3: SEVERE

SIGNS RECORDED-

Global clinical score of signs were observed and documented at baseline and then as each follow up visit.

The conjunctival hyperemia, iris color change, periocular skin pigmentation, growth of eyelashes, corneal staining, verticillata signs was recorded.

GRADE 0: NONE
GRADE 1: MILD
GRADE 2: MODERATE
Grade 3: SEVERE

Mean: To obtain the mean, the individual observations were first added together and then divided by the number of observations. The operation of adding together or summation is denoted by the sign Σ.

The individual observation is denoted by the sign X, number of observations denoted by n, and the mean by $\overline{X}$.

$$\overline{X} = \frac{\Sigma X}{\text{No. of observations (n)}}$$

Results:

Distributions of patients of primary open angle glaucoma and Ocular hypertension into Base line IOP 22-25mmhg (group 1) and Base line IOP 26-30mmhg (group 2) are shown in Table 1 and Figure 1. Out of 34, total 23 (67.65%) patients were included in group 1 and 11 (32.35%) patients were included in group 2.

Table 1: Distribution of patients according to IOP in groups.

Groups	Number of patients (N)
Group1 (Base line IOP 22-25 mmHg)	23 (67.65%)
Group2 (Base line IOP 26-30 mmHg)	11 (32.35%)

The comparisons of mean age of Primary open angle glaucoma and Ocular hypertension patients in between group 1 and group 2 are shown in Table 2 and Figure 2. Values are expressed as mean, median, ±SD, minimum and maximum. Range of age was 42 to 65 years in group 1 and 33 to 64 years in group 2. The mean age was 58.30±6.98 in group 1 and 55.29±8.03 in group 2. The mean age was not significantly different in between groups.

Table 2: Comparison of mean age of Primary open angle glaucoma and Ocular hypertension patients in between group 1 and group 2.

	Mean	Median	Std. Deviation	Minimum	Maximum

Group 1	58.30	60.50	6.98	42	65
Group 2	55.29	57.50	8.03	33	64
	t=1.00, p=0.325				

Table 3: Comparisons of mean IOP in between group 1 and group 2 at baseline to 3 months follow up [Day diurnal variation test (day DVT)].

Table3 comparisons of mean IOP in between group 1 and group 2 at baseline to 3 months follow up [Day diurnal variation test (day DVT)]. The mean IOP at baseline, 2 week, 6 week and 3 months were 23.65±1.43, 16.84±1.95, 14.32±2.54 and 12.23±2.26 in right eye and 23.30±1.66, 16.96±2.2, 14.41±2.48, 12.23±2.23 in let eye in group 1 and 27.09±2.26, 19.88±3.02, 16.91±3.39 and 14.55±3.7 in right eye and 28.18±1.66, 20.48±3.29, 16.91±3.2 and 14.36±3.32 in left eye in group 2, respectively. The mean IOP was significantly more in group 2 as compared to group 1 at baseline to 3 months follow-up in right eye and left eye.

Mean IOP (mmHg)		**Group 1 (n=23)**	**Group 2 (n=11)**	**t**	**p-Value**
		Mean ± SD	**Mean ± SD**		
Baseline	**RE**	23.65 ± 1.43	27.09 ± 2.26	-5.41	<0.001*
	LE	23.30 ± 1.66	28.18 ± 1.66	-8.00	<0.001*
at 2 weeks	**RE**	16.84 ± 1.95	19.88 ± 3.02	-3.54	0.001*
	LE	16.96 ± 2.2	20.48 ± 3.29	-3.71	0.001*
6 weeks	**RE**	14.32 ± 2.54	16.91 ± 3.39	-2.49	0.018*
	LE	14.41 ± 2.48	16.91 ± 3.2	-2.51	0.017*
3 months	**RE**	12.23 ± 2.26	14.55 ± 3.7	-2.26	0.031*
	LE	12.23 ± 2.23	14.36 ± 3.32	-2.22	0.034*

Table 4: Comparisons of drug use in group 1 and group 2

Table 4 and Figure 8 show the comparisons of drug use in group 1 and group 2. The percentage of number of patients used Bimatoprost and Netarsudil drug were 52.17% and 47.83% in group 1 and 45.45% and 54.55% in group 2, respectively. The percentage of number of patients used Bimatoprost and Ripasudil drug were not significantly different in between groups.

	Group 1 (n=23)	**Group 2 (n=11)**	**OR (95% CI)**	**p-value**
Bimatoprost	12 (52.17%)	5 (45.45%)	1.31 (0.31-5.14)	0.714
Ripasudil	11 (47.83%)	6 (54.55%)		

Table 5 shows the correlation in between grading with IOP at baseline to 3 months follow-up in overall patients. The grading was not significantly correlated with change in IOP at baseline, 2 weeks, 6 weeks and 3 months.

Table 5: Correlation of IOP between at baseline to 3 months follow-up in overall patients.

Intraocular pressure (IOP)	**Pearson Correlation**	**p-Value**

at baseline	RE	-0.119	0.502
	LE	-0.195	0.268
at 2 weeks	RE	0.584	0.001*
	LE	0.369	0.014*
at 6 weeks	RE	0.536	<0.001*
	LE	0.319	0.035
at 3 months	RE	0.457	<0.001*
	LE	0.488	<0.001*

Discussion: For the treatment of POAG and OHT, rho kinase (ROCK) inhibitors have been demonstrated in preclinical trials to decrease IOP by enhancing trabecular outflow capability. In two Phase 3 noninferiority studies, the Rho kinase and nor-epinephrine transporter inhibitor Netarsudil significantly reduced IOP compared to timolol in patients with POAG or OHT, and the US Food and Drug Administration approved it in December 2017 for the treatment of elevated IOP in those patients.[28]. In those studies, Ripasudil was shown to decrease IOP by increasing trabecular outflow facility and by reducing aqueous humour production.[54] The aim of this study was the IOP lowering efficacy and adverse effects of Ripasudil 0.02% and bimatoprost 0.01% in in Primary open angle glaucoma and Ocular hypertension.

In our study total 50% patients used bimatoprost and 50% patients used Ripasudil drug. Moreover, the percentage of number of patients used bimatoprost and Ripasudil drug were 52.17% and 47.83% in base line IOP 22-25mmhg group and 45.45% and 54.55% in base line IOP 26-30mmhg group, respectively.

In this study the bimatoprost and netarsudil drugs were significantly reduced the IOP from baseline to 3 months follow-up in both the groups. Numerous prior observational studies have shown that bimatoprost 0.01% is well tolerated and effective at lowering IOP.[60] Patients with POAG or OHT who had never received treatment benefited from an IOP reduction of 30% over the course of 12 weeks in a clinical practise setting, with 93% of patients suffering mild, trace, or no hyperaemia.[18] In patients who switched from prior medication, bimatoprost 0.01% was well tolerated and related with an additional 10%–15% reduction in IOP.[25] In a comprehensive observational trial with more than 10,000 patients, bimatoprost 0.01% significantly reduced mean IOP from a baseline of 20.1–4.5 mmHg in all study participants and from 20.1–6.5 mmHg in patients who had not previously received treatment.[72] In comparison to bimatoprost 0.03%, Bimatoprost 0.01% has shown equal IOP-lowering efficacy and enhanced tolerability, including less frequent and severe conjunctival hyperaemia.[46] bimatoprost 0.01% is equal to bimatoprost 0.03% in terms of effectiveness for decreasing IOP throughout a 12-month treatment period, according to research by Katz et al. [44] bimatoprost 0.01% demonstrated better patient adherence than bimatoprost 0.03% in prior observational research.[72] Adherence in the current study was better than or equal to that of the previous therapy in more than 97% of patients who switched from a previous therapy to bimatoprost 0.01%. The mean IOP for the treatment group changed by around 20% as a result of Netarsudil treatment. While tests on normotensive monkeys revealed a significantly bigger increase, 53% at 6 hours after a single injection, the degree of the impact appears to vary by species. Animal studies also demonstrated an increase in outflow facility with Netarsudil therapy.[31] However, the Netarsudil concentration in that trial was higher (0.04% vs. 0.02% in our investigation), and two drops rather than one were administered to each eye. In this study both bimatoprost and netarsudil showed significant decrease in IOP, however, bimatoprost was found to be more effective in decreasing IOP in all patients as compared to netarsudil especially more in higher base line group.

Conclusion: This study was carried out to compare IOP lowering efficacy and adverse effects of Netarsudil 0.02% and bimatoprost 0.01% in Primary open angle glaucoma and Ocular hypertension. For this purpose, a prospective study was carried out that included a total 34 patients during this study period. Out of 34, total 23 (67.65%) patients had base line IOP 22-25mmHg and 11 (32.35%) patients had base line IOP 26-30 mmHg. The following findings from the study were drawn. Bimatoprost and Ripasudil drugs significantly reduced the IOP from baseline to 3 months follow up in both lower base line IOP and higher base line IOP group. Bimatoprost was found to be more effective in decreasing IOP in all patients as compared to Netarsudil especially more in higher base line IOP group.The conjunctival hyperemia, conjunctival hemorrhage, cornea verticillata and erythema of eyelid were found in 35.29%, 5.88%, 5.88%, and 5.88% patients in bimatoprost group and 47.06%, 11.76%, 11.76% and 5.88% patients in Ripasudil drug group. On the basis on signs, both drugs group were comparable. The pruritus was found in 11.76% and burning and stinging pain was 17.65% in bimatoprost group whereas 17.65% and 29.41% in Ripasudil drug group. On the basis on symptoms, both drugs group were comparable.

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