A STUDY OF EFFICACY OF PROSTAGLANDIN ANALOGUES IN COMPARISON WITH TIMOLOL MALEATE AS FIRST DRUG OF CHOICE IN THE TREATMENT OF PRIMARY OPEN-ANGLE GLAUCOMA

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ABSTRACT

BACKGROUND

Glaucoma is an ischaemic optic neuropathy comprising of three entities; one is raised intraocular pressure, second one is optic disc changes and third one is visual field defects. Intraocular pressure remains the major modifiable risk factor.

The aim of the treatment is to lower the IOP and thereby prevent the significant functional visual defect and preserve the visual function.

MATERIALS AND METHODS

The current study is a prospective hospital-based observational study conducted over a period of two years in a sample of 50 patients attending the Outpatient Department, Department of Ophthalmology, Rangaraya Medical College, Government General Hospital, Kakinada, Andhra Pradesh.

RESULTS

A study of efficacy of prostaglandin analogues in comparison with timolol maleate as first drug of choice in the treatment of primary open- angle glaucoma.

CONCLUSION

According to the study, prostaglandin analogues showed higher efficacy in reducing the intraocular pressure as compared to that of the timolol maleate.

KEYWORDS

Glaucoma, Timolol Maleate, Latanoprost, Intraocular Pressure.

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BACKGROUND

Glaucoma is a chronic, progressive optic neuropathy caused by a group of ocular conditions, which lead to damage of the optic nerve with loss of visual function. Because the disease is treatable and because the visual impairment is caused by glaucoma is irreversible, early detection is essential.

Early diagnosis depends on the examination of the optic disc, retinal nerve fibre layer, measurement of intraocular pressure and visual field. Newer imaging and psychophysical tests can improve both detection and monitoring of the progression of the disease.

Recently completed long-term clinical trials provide convincing evidence that lowering intraocular pressure prevents the progression at both the early and late stages of the disease. IOP is the only modifiable risk factor for glaucoma.[1-4]

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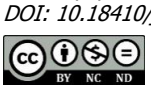

Several ocular conditions have been implicated as risk factors associated with glaucomatous optic nerve damage.

These Conditions Include-

1. Elevated IOP.
2. Older age.
3. Family history of glaucoma.
4. Thinner central corneal thickness.

As it is a painless loss of vision, by the time the patient develops symptoms, it becomes late and 40% of the fields will be lost. Therefore, it is important to screen the patients who are at risk. Early diagnosis prevents the further loss of the visual field. The four important means of diagnosis are IOP measurement, gonioscopy fundus examination and visual field testing. Treatment of glaucoma should be instituted as soon as the definitive diagnosis is made. The glaucomas can be treated by medical, laser and surgical means. The initial treatment is generally medical. A target pressure has to be defined for each patient.

Glaucomatous visual field changes and defects are almost irreversible with the visual field changes of glaucoma being noticed by the patient after significant disease progression due to a relative lack of alerting symptoms. Reduction of elevated Intraocular Pressure (IOP) is the only as yet proven approach to protect against

visual field loss in patients with Primary Open-Angle Glaucoma (POAG) or Ocular Hypertension (OHT).

When they first entered the ophthalmic pharmacotherapy about 20 years ago, prostaglandins were viewed as a potential first-line therapy for glaucoma patients. Yet in less than a decade, glaucoma specialists' preferences have changed with most reporting that they prefer prostaglandins over beta blockers as their patients' initial medication.

Latanoprost (0.005%) has truly withstood the test of time and has indeed proved to be one of the best antiglaucoma medications when used as monotherapy or as adjunctive therapy. Bimatoprost 0.01% has a similar overall safety profile, a favourable hyperaemia profile and less overall discontinuation compared with bimatoprost 0.03%. In lieu of its poor efficacy, unoprostone (0.015) has lost its hold in the antiglaucoma palate. Travoprost (0.004%) in which benzalkonium chloride is replaced with sofZia, a robust ionic buffered preservative system that is gentle to the ocular surface. Tafluprost, the newest addition to the prostaglandin brigade is a fluorinated analogue of prostaglandin-F 2α and is available as a sterile ophthalmic solution of 0.0015% (0.015 mg/mL) being approved by the US-FDA on 10th February 2012.

A new futuristic glaucoma therapeutic management paradigm where clinical success is no longer simply measured by achieved level of intraocular pressure control, but also long-term preservation of visual function and patient's quality of life is expected to dramatically improve upon current treatment algorithms for ocular hypertension and glaucoma. Patients with OAG, every 1 mmHg of IOP-lowering results in an estimated 10% to 19% reduction in the risk of visual field progression.[3,5,6]

The study is aimed at studying the efficacy of prostaglandin analogues (latanoprost 0.005%) in comparison with timolol maleate as first drug of choice in the treatment of primary open-angle glaucoma.

Common initial intervention in patients with OAG,[7] while patients with elevated IOP often initiate treatment with monotherapy, many will require patients with OAG who achieve target IOP lowering demonstrate a significantly lower risk of disease progression.[2] Pharmacological lowering of IOP is the most common treatment.

Selecting IOP lowering agent to achieve and maintain target IOP.[1,8,9]

Aims and Objectives

Glaucoma is an ischaemic optic neuropathy comprising of three entities; one is raised intraocular pressure, second one is optic disc changes and third one is visual field defects.

Intraocular pressure remains the major modifiable risk factor. The aim of the treatment is to lower the IOP and thereby prevent the significant functional visual defect and preserve the visual function.

POAG is a chronic bilateral, often asymmetrical disease in adults featuring acquired loss of optic nerve fibres and abnormality in the visual field with an open anterior chamber angle and an IOP often over 21 mmHg.

Aims

The aim of the study is to study the effect of prostaglandin analogues in comparison with timolol maleate in lowering the intraocular pressure in patients of primary open-angle glaucoma.

Objectives

- Setting a target pressure to the POAG patients.
- To study the effect of timolol maleate in lowering the intraocular pressure in the patients of primary open-angle glaucoma.
- To study the effect of prostaglandin analogues (latanoprost 0.005%) in lowering the intraocular pressure in the patients of primary open-angle glaucoma.
- To study the effect of prostaglandin analogues in lowering the intraocular pressure in comparison with timolol maleate in the patients of primary open-angle glaucoma.

MATERIALS AND METHODS

Design

Prospective, hospital-based, interventional study.

Source and Procedure

The current study is a prospective hospital- based observational study conducted over a period of two years in a sample of 50 patients attending the Outpatient Department, Department of Ophthalmology, Rangaraya Medical College, Government General Hospital, Kakinada, Andhra Pradesh.

Duration of Study

18 months (February 2016 to July 2017).

Sample Size

A convenient sample size of 50 cases were taken, out of which 25 cases each were assigned into 2 groups for the ease of the study.

Inclusion Criteria

1. Patients of age 40 years and above, patients with family history of primary open-angle glaucoma.
2. IOP >21 mmHg in an eye without antiglaucoma medication.
3. Appearance of optic disc changes suggestive of glaucoma.
4. Asymmetric cupping between the two eyes.
5. Visual field defects suggestive of glaucomatous changes.

Exclusion Criteria

1. Patients previously diagnosed to have glaucoma and on medication.
2. Angle-closure glaucoma.
3. Patients with history of other intraocular diseases.
4. Patients with secondary glaucomas.
5. Patients with complicated intraocular surgery.

6. Other diseases affecting visual fields; e.g. pituitary lesions, demyelinating diseases and other neurological diseases.
7. Patients who were not willing to participate in the study.

After obtaining approval of the Institutional Ethics Committee, a written informed consent was taken from patients in his/her vernacular language. A thorough clinical history was taken regarding chief complaint, duration of disease and any other relevant history.

A Complete Ophthalmic Examination was done to every Patient including-

1. General examination, ocular examination.
2. Best corrected visual acuity, refraction.
3. Anterior segment evaluation by complete slit-lamp biomicroscopy.
4. IOP values by standard Goldmann applanation tonometer.
5. Gonioscopy by Goldmann indirect gonioscope.
6. Visual field assessment by Humphrey Field Analyser II, Carl Zeiss Meditec.
7. Posterior segment evaluation done by +78D/+90D biomicroscopy, indirect ophthalmoscopy and fundus photography.

Follow Up

- The patients were followed up at the end of 1st, 2nd, 3rd months.
- They were asked for any new complaints at each visit.
- Visual acuity at each visit is assessed.
- Anterior segment evaluation, gonioscopy, IOP measurement with applanation tonometer were performed at each visit.
- Dilated fundus examination was performed.

Statistical Analysis

- The primary efficacy outcome was mean diurnal IOP reduction from the baseline to the end of 12 weeks.
- Secondary efficacy outcome was the difference in the percentage of patients reaching the target IOP between the two groups.
- The two groups were compared with each other in mean IOP reduction using the paired Student's t-test. The level of significance was set to P <0.05%.
- SPSS software was used for the statistical analysis of the data.

RESULTS

Present study, i.e. a study of efficacy of prostaglandin analogues in comparison with timolol maleate as first drug of choice in the treatment of primary open-angle glaucoma is a hospital-based, prospective, interventional study conducted on patients attending the Ophthalmology Outpatient Department, Government General Hospital, Kakinada, A.P. for a period of 2 years. A total of 100 eyes of 50 cases were studied.

Observations and Inferences of the Study were as following-

Age Distribution of Patients

Mean age of patients in present study was 55.38 years ranging from 40-72 years.

Mean	N	Standard Deviation
52.9200	25	9.86864

Table 1. Mean Age of Timolol Group (Group 1)

Mean Age	N	Standard Deviation
57.8400	25	8.97181

Table 2. Mean Age of Prostaglandin Analogues Group (Group 2)

Age Distribution of Patients

The range of age of patients included in the study was 40 years to 72 years. The maximum number of patients falling in the group of 60-64 years. Minimum number of patients in group of 65-69 years.

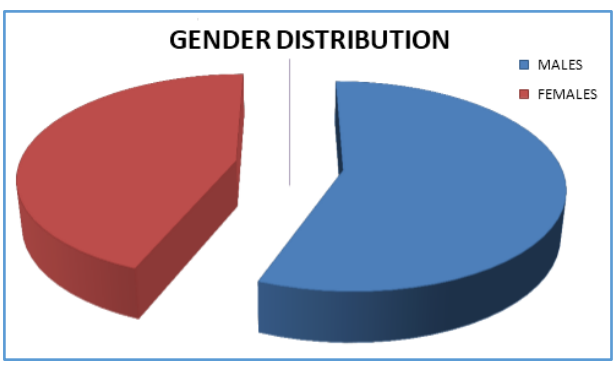

Figure 1. Gender Distribution

Age Distribution	Group 1 (Timolol)	Group 2 (PG Analogues)	Total
40-44 years	3	4	7
45-49 years	2	8	10
50-54 years	3	3	6
55-59 years	5	3	8
60-64 years	7	4	11
65-69 years	1	2	3
70-74 years	4	1	5

Table 3. Age Distribution

Mean age of the patients in the study was 55.38 years.

Maximum number of patients were falling in the age group of 60-65 years (mode of the study) 11 patients out of 50 fall in the age group category of 60-64 years, which accounts for 22% of the patients participating in the study. 31 patients are falling under the age of <60 years, which accounts for 62% and number of patients >65 years are 19, which accounts for 38%.

Gender Distribution of Participants

- Number of males in the study were 28.
- Number of females were 22.

Group	Number of Males	Number of Females
Group 1	13	12
Group 2	15	10
Total	**28**	**22**
Percentage	**56%**	**44%**

Table 4. Distribution of Gender

As shown in Table 4 in the both groups, the majority were males of about 28 in number accounting for 56% and females were 22 accounting for 44%.

Allocation of Patients into Two Groups

- The patients were randomly allotted into two groups.
- Group 1 were treated with timolol and Group 2 were treated with prostaglandin analogues.

Group	Drug	Number of Patients	Number of Eyes
Group 1	Timolol	25	50
Group 2	PG analogues	25	50

Table 5. Allocation of Patients into Two Groups

BCVA	Group 1	Group 2	Total
6/6 - 6/12	18	19	**37**
6/18 - 6/36	21	15	**36**
6/60 and less	11	16	**27**

Table 6. Best-Corrected Visual Acuity (BCVA)

37% of the eyes of the participating in the study had the BCVA better than 6/12, 36% had better than 6/36 and 27% had the BCVA worse than 6/60 as shown.

Group	Mean	N	Standard Deviation
Group 1	0.6180	50	0.11899
Group 2	0.6840	50	0.02828

Table 7. Cup:Disc Ratio

100 eyes of 50 patients participating in the two groups were examined and the mean cup-to-disc ratio of 50 eyes each in the two groups were calculated. As shown in table 7, the mean cup-to-disc ratio of group 2 receiving prostaglandin analogues had higher C:D ratio as compared to that of timolol group with 0.618 in Group 1 and 0.684 in Group 2.

Group	Mean Baseline IOP	N	Standard Deviation
1	22.3200 mm of Hg	50	0.36365
2	25.7600 mm of Hg	50	0.36365

Table 8. Mean Intraocular Pressure at the Time of Presentation

The IOP of 50 eyes in each group were measured using applanation tonometer and the mean IOP of 50 eyes in each group were calculated separately. As shown in Table 8, mean IOP of group was greater in Group 2 than Group 1 with 22.32 mm of Hg in the timolol group and 25.76 mm of Hg in the prostaglandin analogues group.

Mean Intraocular Pressure at 1st, 2nd and 3rd Follow Up Visits in Group 1- Table No. 9

Mean IOP of 50 eyes at the presentation in the group receiving timolol maleate (Group 1) is 22.32 mm of Hg. IOP at the 1st follow up was reduced by 1.34 mm of Hg with standard deviation of 0.363655, which accounts for the 6% of baseline IOP. IOP at the 2nd follow up was reduced by 2.28 mm of Hg with a standard deviation of 0.42426, which accounts for 10.21% of the baseline IOP. At the end of 12 weeks with difference of mean of 4.6 mm of Hg with standard deviation of 0.30305, which accounts for the 18.81% as shown in the Table 9.

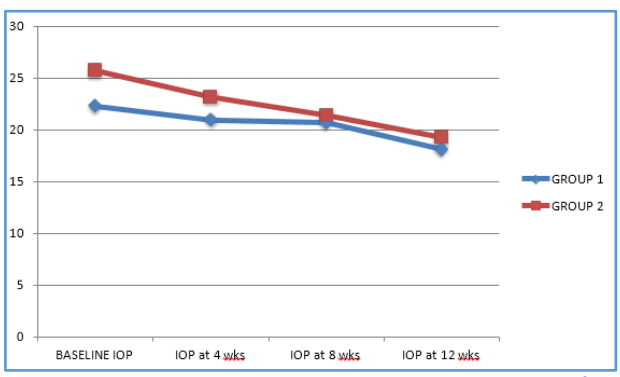

Figure 2. Mean Intraocular Pressure at 1st, 2nd and 3rd Follow up Visits in Group 1 and Group 2

	IOP at Presentation	1st Followup	2nd Followup	3rd Followup
Mean	22.32 mm of Hg	20.98 mm of Hg	20.04 mm of Hg	18.12 mm of Hg
N	50	50	50	50
Standard deviation	0.363655	0.42426	0.44447	0.30305

Table 9. Mean Intraocular Pressure at 1st, 2nd and 3rd Follow up Visits in Group 1

Mean Intraocular Pressure at *1st, 2nd and 3rd* Follow Up Visits in Group 2

Mean IOP at the presentation in the group receiving prostaglandin analogues is 25.76 mm of Hg. IOP at the 1st follow up was reduced by 2.54 mm of Hg with standard deviation of 0.42426, which accounts for the 9.86% of baseline IOP. IOP at the 2nd follow up was reduced by 4.32 mm of Hg with a standard deviation of 0.44447, which accounts for 16.77% of the baseline IOP. At the end of 12 weeks with difference of mean of 6.46 mm of Hg with standard deviation of 0.30305, which accounts for the 25.07% as shown in the Table 9.

	IOP at Presentation	1st Followup	2nd Followup	3rd Followup
Mean	25.76 mm of Hg	23.22 mm of Hg	21.44 mm of Hg	19.30 mm of Hg
N	50	50	50	50
Standard deviation	0.363655	0.42426	0.44447	0.30305

Table 10. Mean Intraocular Pressure at 1st, 2nd and 3rd Follow Up Visits in Group 2

	IOP at Presentation	IOP at 3rd Followup	Percentage of Reduction of IOP
Group 1	22.32 mm of Hg	18.12 mm of Hg	18.81%
Group 2	25.76 mm of Hg	19.30 mm of Hg	25.07%
Table 11. Percentage of Reduction of IOP			

As shown in the Table 11, the percentage of reduction of IOP as compared to baseline IOP was more in group 2 receiving prostaglandin analogues was higher than that of group 1 receiving timolol. The reduction of IOP was 18.81% in group 1 and 25.07% in group 2.

Paired t-Test for Group 1

The mean of difference of IOP from the baseline to that of the 3rd follow up visit was 4.58 with a p-value, p of <0.5%, standard deviation of 0.50508 and standard error of 0.07413. The established 95% confidence interval levels of the mean of difference before and after treatment with timolol maleate were with upper limit of 4.4346 and lower limit of 4.72354 as shown in Table 12.

The mean of difference of IOP from the baseline to that of the 3rd follow up visit was 6.46 with a p-value, p of <0.5%, standard deviation of 0.6667 and standard error of 0.09429. The established 95% confidence interval levels of the mean of difference before and after treatment with prostaglandin analogues were with upper limit of 6.27053 and lower limit of 6.64947 as shown in Table 13.

Complications	Group 1	Group 2
Conjunctival hyperaemia	1 (4%)	3 (12%)
SPK	-	-
Eye irritation	2 (8%)	1 (4%)
Watering	2 (8%)	2 (8%)
Headache and eye pain	-	-
Iris pigmentation	-	-
Eyelash growth	-	-
Table 12. Ocular Complications		

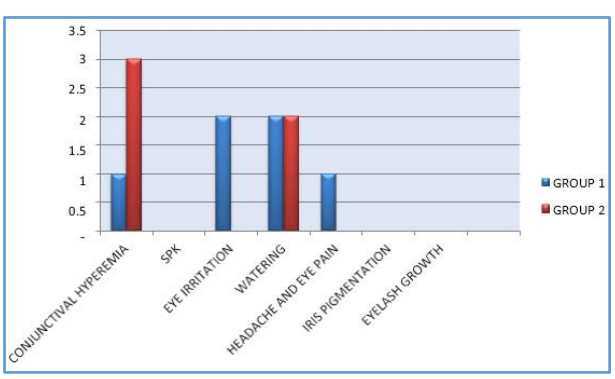

Figure 3. Ocular Complications

DISCUSSION

About 75 subjects were screened in this study, 25 subjects were excluded and 50 were diagnosed as primary open-angle glaucoma and assigned in this study. 50 newly-diagnosed patients of primary open-angle glaucoma were enrolled in the study.

The patients were allotted into 2 groups: Group - 1- Patients were given timolol maleate 0.5% twice daily 12 hours apart; Group - 2- Patients were given prostaglandin analogues like latanoprost 0.005% (or) travoprost 0.04% (or) bimatoprost 0.015% once daily to be administered at the bedtime.

Sex Distribution

Out of 50 patients, 56% were males and 44% were females. Males were at greater risk for development of POAG than females.

Gender	Present Study
Males	56%
Females	44%
Table 13. Gender Distribution	

Among the participants in the study, 28 (56%) were males and 22 (44%) were females.

Baseline IOP	Present Study
Group 1	22.32 ± 0.36 mm of Hg
Group 2	25.76 ± 0.363 mm of Hg
Table 14. Mean Baseline IOP	

The mean baseline pretreatment IOP is more or less similar in the groups receiving prostaglandin analogues in both studies.

IOP	Present Study
Group 1	20.98 +/- 0.42426 mm of Hg
Group 2	23.22 +/- 0.424 mm of Hg
Table 15. IOP at the End of 4 Weeks	

IOP	Present Study
Group 1	20.04 +/- 0.4447 mm of Hg
Group 2	21.44 +/- 0.4447 mm of Hg
Table 16. IOP at the End of 8 Weeks	

IOP	Present Study
Group 1	18.12 ± 0.30305 mm of Hg
Group 2	19.30 ± 0.30305 mm of Hg
Table 17. IOP at the End of 12 Weeks	

The percentage reduction of IOP in the present study was 18.81%.

The mean baseline IOP of group 2 receiving the prostaglandin analogues in the present study was 25.76 mm of Hg. The reduction in the mean IOP of the group was 6.46 mm of Hg at the end of 12 weeks, which accounts for 25.07% of the baseline IOP.

The percentage reduction of IOP in the present study was 25.07% common initial intervention in patients with OAG.[7] While patients with elevated IOP often initiate treatment with monotherapy, many will require patients with OAG who achieve target IOP lowering demonstrate a significantly lower risk of disease progression.[2] Pharmacological lowering of IOP is the most common treatment IOP lowering agent to achieve and maintain target IOP.[1,8,9]

CONCLUSION

In this study, 50 newly-diagnosed patients of primary open-angle glaucoma were allotted into two groups. Group 1 received timolol maleate and the Group 2 received prostaglandin analogues. The two groups were followed for every 4 weeks up to 12 weeks.

According to the study, prostaglandin analogues showed higher efficacy in reducing the intraocular pressure as compared to that of the timolol maleate.

Moreover, this group 2 has advantages of once a day dosing of the drug, which plays a major role in the compliance, its potency, efficacy during day and night, mechanism of action on outflow and probable safer systemic side effect profile.

Even though the prostaglandin analogues were proven to be efficient, their main drawback is their cost, which plays major role in developing countries like India. The percentage reduction of IOP of timolol is 18% in the study and that of the prostaglandin analogues is 25%.

However, in the developing countries like India, timolol is made available to the general patients with advantage of being available in preservative-free form at affordable prices.

In conclusion, as per the Indian scenario is concerned, management of glaucoma with timolol as a single drug is effective and affordable to the patient. In the patients who require the greater control of IOP to achieve the target IOP, prostaglandin analogues would be the better choice due to its greater efficacy.

Hence, prostaglandin analogues can be employed to all affordable patients as the first line therapy as it is most effective single-drug regimen with greater control of IOP, once daily dosing and minimal systemic side effects.

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