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Head To Head Comparasion of Topical Timolol (0.5%) + Bimatoprost (0.03%) Versus Topical Timolol (0.5%) + Dorzolamide (2%) In Primary Open-Angle Glaucoma

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Abstract
Primary open-angle glaucoma (POAG) is the second leading cause of blindness in the world, and third most common cause of blindness in India and its prevalence always increases with age. For larger intraocular pressure reduction, combination therapy with two drugs is required. To this purpose we compared the efficacy, safety and tolerability of fixed combination of topical Bimatoprost (0.03%) and Timolol (0.5%) with topical Dorzolamide (2%) and Timolol (0.5%) fixed combination in lowering intra ocular pressure in patients with primary open-angle glaucoma. This prospective randomised interventional study was conducted at a Medical college near Vijayawada over the period of 3 years. The total number of patients enrolled in this study was 60, and the number of patients in each treatment group was 30. After a thorough screening, one group was prescribed Timolol (0.5%) – Dorzolamide (2%) ophthalmic solution one drop twice daily, and similarly, the other group was prescribed Timolol (0.5%) - Bimatoprost (0.03%) ophthalmic solution one drop once daily in the morning. At each follow-up visit local and systemic adverse effects that occurred during the treatment period were recorded. Adverse effects were evaluated by asking patients a general query about their state of health. Patients were also queried regarding their compliance to the study medicine at each follow-up visit. Efficacy within the group is measured by comparing the mean IOP of each follow-up visit with the mean IOP of baseline visit in the same treatment group (either T-D/ T-B) and comparing both the significance in the difference of both the means by Student's t- test (paired t-test). Efficacy between the two treatment groups is measured by comparing the mean IOP of both the treatment groups (T-D & T-B) at each visit starting from visit 0 (baseline) and comparing the significance of the difference between the means of two groups by Student's t- test (Unpaired t-test). Safety is assessed by calculating the percent incidence of each adverse effects of each preparation. Tolerability is assessed by measuring the compliance of patients in each treatment group. Total 55 patients, clinically diagnosed with POAG were analysed in detail for the effect of above-fixed drug combination medications, at the end of 12 weeks. At 12 weeks, the mean IOP value for both the treatment groups is as follows: -p-value of paired t-test at 12 weeks for the T-D group is 0.002 (p<0.01), which is highly statistically significant. P value for the T-B group is 0.002 (p<0.01), which is also highly statistically significant. The p-value of unpaired t-test between two treatment groups at 12 weeks is 0.0007 (p<0.001), which is highly statistically significant. Hence, Timolol+Bimatoprost fixed combination was more efficacious and safe compared to Timolol+Dorzolamide fixed combination in the treatment of primary open-angle glaucoma

Keywords: Primary open-angle glaucoma (POAG), Timolol, Bimatoprost, Dorzolamide, Fixed dose

Introduction
Primary open-angle glaucoma (POAG) is a chronic, progressive optic neuropathy, characterised by morphological changes at the optic nerve head and retinal nerve fibre layer in the absence of other ocular diseases or congenital anomalies and the vision loss is asymptomatic and irreversible [1] Glaucoma is the second leading cause of blindness in the world, and third most common cause of blindness in India and its prevalence always increases with age. [2-3]. However, blindness due to glaucoma is preventable for which early detection and treatment is necessary [4]. The most common and modifiable risk factor known is a raised intraocular pressure, prevention of this is the major goal in the management of glaucoma [5] Timolol, a non-selective β- blocker is the gold standard treatment option in primary open-angle glaucoma followed by Prostaglandin analogues. For larger intraocular pressure reduction, combination therapy with two drugs is required [6] for a combination therapy to be clinically advantageous, it must increase efficacy beyond each of its individual components given

as Monotherapy without lessening safety. [7] To this purpose we compared the efficacy, safety and tolerability of fixed combination of topical Bimatoprost (0.03%) and Timolol (0.5%) with topical Dorzolamide (2%) and Timolol (0.5%) fixed combination in lowering intra ocular pressure in patients with primary open-angle glaucoma.

Methods

This prospective randomised interventional study was conducted at Dr Pinnamaneni Siddartha Institute of medical sciences and research foundation, Chinaoutpalli, Gannavaram over the period of 3 years during 2010 and 2012. The Study protocol was approved by ethics committee and obtained patient informed consent. Both male and female patients aged above 35 yrs with clinically diagnosed primary open-angle glaucoma attending the outpatient department of ophthalmology were included in this study. The total number of patients enrolled in this study was 60, and the number of patients in each treatment group was 30. Patients with raised IOT ≥22 mmHg at baseline, glaucomatous optic atrophy with or without typical glaucomatous field damage were included. Patients with contraindications to beta-blocker therapy-Bronchial asthma chronic obstructive pulmonary disease, bradycardia, heart block, and cardiac failure, DM, and HTN with functionally significant visual loss within the past one year were excluded from the study.

After a thorough screening, one group was prescribed Timolol (0.5%) – Dorzolamide (2%) ophthalmic solution one drop twice daily, and similarly, the other group was prescribed Timolol (0.5%) - Bimatoprost (0.03%) ophthalmic solution one drop once daily in the morning.

Visit - 0: At visit 0, systemic as well as ophthalmic history was taken from the patients. Snellen's visual acuity and intraocular pressure were measured. Slit lamp biomicroscopy was done and the optic nerve head evaluated. This was followed by Perimetry for the evaluation of visual fields. Patients who met the inclusion criteria and not having any exclusion criteria were taken in the present study.

Patients were randomly assigned to receive either the topical 0.03% Bimatoprost - 0.5% Timolol fixed combination (T-B) once daily or topical 2% Dorzolamide - 0.5% Timolol fixed combination (T-D) twice daily. Patients were instructed regarding correct medication instillation. All patients were instructed to occlude the punctum and perform nasolacrimal occlusion and eyelid closure for at least 3 minutes after instillation of each study eye drop.

Safety visit: For all patients safety evaluation was performed after two weeks of treatment- safety visit, which included questioning for adverse effects, observing and recording adverse effects.

First follow- up visit: For the first follow-up visit, patients were asked to come two weeks after safety visit. Thus, first follow- up is conducted four weeks after visit 0. In this visit, the IOP is measured and visual acuity, slit lamp biomicroscopy were performed.

Second follow-up visit: For the second follow– up visit, patients were asked to come after four weeks following the first visit. Thus, second follow- up is conducted eight weeks after visit 0. In this visit, the IOP is measured, and Snellen's visual acuity and slit lamp biomicroscopy were performed.

Third follow- up visit: For the third follow– up visit, patients were asked to come after four weeks following the second visit. Thus, third follow- up is conducted 12 weeks after visit 0. In this visit, the IOP is measured, and Snellen's visual acuity and slit lamp biomicroscopy were performed. Perimetry was performed for the evaluation of visual fields.

At each follow-up visit local and systemic adverse effects that occurred during the treatment period were recorded. Adverse effects were evaluated by asking patients a general query about their state of health. Safety measures included the recording of systemic adverse reactions, vitals and local ocular complaints like itching, congestion, burning, dryness, lacrimation and pigmentation.

Patients were also queried regarding their compliance to the study medicine at each follow-up visit.Clinical examination findings, investigations and relevant history that were obtained from patients were entered in the case-sheet proforma during each visit.

Statistical Analysis

Efficacy within the group: This is measured by comparing the mean IOP of each follow-up visit with the mean IOP of baseline visit in the same treatment group (either T-D/ T-B) and comparing both the significance in the difference of both the means by Student's t- test (paired t-test).

Efficacy between the two treatment groups: This is measured by comparing the mean IOP of both the treatment groups (T-D & T-B) at each visit starting from visit 0 (baseline) and comparing the significance of the difference between the means of two groups by Student's t- test (Unpaired t-test). Safety is assessed by calculating the percent incidence of each adverse effects of each preparation. Tolerability is assessed by measuring the compliance of patients in each treatment group.

Results

Sixty patients were eligible to participate in this study. They were randomised into Timolol-Bimatoprost (T-B) group and Timolol-Dorzolamide (T-D) group, 30 patients in each group.

T-D group, 28 patients completed the study, and two were lost to follow-up. And in the T-B group, 27 patients completed the study, and three were lost to follow-up.

Total 55 patients, clinically diagnosed with POAG were analysed in detail for the effect of above-fixed drug combination medications, at the end of 12 weeks.

Evaluation of efficacy is done by individual assessment of decrease in intraocular pressure at each visit compared to the baseline values. The significance of lowering of intraocular pressure between two treatment groups was compared by calculating 'p' value using Student's t-test.

At four weeks, the mean IOP (mmHg) value for both the treatment groups is as follows: -p-value of paired t-test at four weeks for the T-D group is 0.45, which is not statistically significant. P-Value for Timolol-Bimatoprost group is 0.13, which is also not statistically significant.P value of unpaired t-test between two treatment groups at four weeks is 0.33, which is not significant.

At eight weeks, the mean IOP value for both the treatment groups is as follows: -p-value of paired t-test at eight weeks for the T-D group is 0.01 (p<0.05), which is statistically significant. P value for the T-B group is 0.007 (p<0.01), which is also highly statistically significant.

At 12 weeks, the mean IOP value for both the treatment

groups is as follows: -p-value of paired t-test at 12 weeks for the T-D group is 0.002 (p<0.01), which is highly statistically significant. P value for the T-B group is 0.002 (p<0.01), which is also highly statistically significant. The p-value of unpaired t-test between two treatment groups at 12 weeks is 0.0007 (p<0.001), which is highly statistically significant

Safety

Out of 27 patients in the T-B group, four patients experienced ocular related side effects like burning, stinging, irritation and one patient experienced foreign body sensation. Eight patients had conjunctival hyperaemia, and six patients had pigmentation of the iris. Out of the 28 patients in the T-D group, six patients experienced ocular irritation symptoms like burning, stinging and two experienced foreign body sensation and eight patients had altered taste sensation. All the ocular side effects could be tolerated by the patients and decreased after eight weeks of treatment.

Compliance

Out of 30 patients in the T-D group, two patients could not attend for follow-up and could not complete the study. The compliance in the group is 93.3%.Out of 30 patients in the T-B group, three patients could not attend for follow-up and could not complete the study. The compliance is 90%. The follow-up was regular in both the treatment groups.

Table 1: Demographic Profile of patients

31-40	2	3.63%
41-50	6	10.90%
51-60	17	30.90%
61-70	16	29.09%
71-80	14	25.45%
TOTAL	**55**	**100%**
Males	34	61.82%
Females	21	38.18%
Total	**55**	**100%**
Family history	**No. of subjects**	**Percentage**
Positive	13	23.60%
Negative	42	76.60%
Total	55	100%
Prevalence of Visual Field Defects **Type of scotoma**	**No. of subjects**	**Percentage**
Biarcuate	22	40%
Paracentral	15	27.27%
Arcuate	13	23.63%
Tubular	5	9.09%
Total	**55**	100%

Table 2: Effect of T-D versus to T-B and responders

		T-D		**T-B**		**% Reduction**	
IOP (0 wks)		29.94+/−2.78		29.78+/−2.59			
4 Weeks							
T-D		29.94+/−2.78		23.92+/−2.22		20.10%	
T-B		29.78+/−2.59		23.64+/−2		20.60%	
8 Weeks							
T-D		29.94+/−2.78		21.48+/−1.96		28.25%	
T-B		29.78+/−2.59		20.89+/−1.69		29.85%	
12 Weeks							
T-D		29.94+/−2.78		17.46+/−1.33		41.6%	
T-B		29.78+/−2.59		15.84+/−1.02		46.80%	
comparison of the percentage of patients reaching target IOP after 12 wks							
IOP (mmHg)	<15	<16	<17	<18	<19	<20	Total
T-D	0%	14.10%	21.80%	25%	21.40%	17.70%	100%
T-B	18.60%	37%	29.60%	14.80%	0%	0%	100%

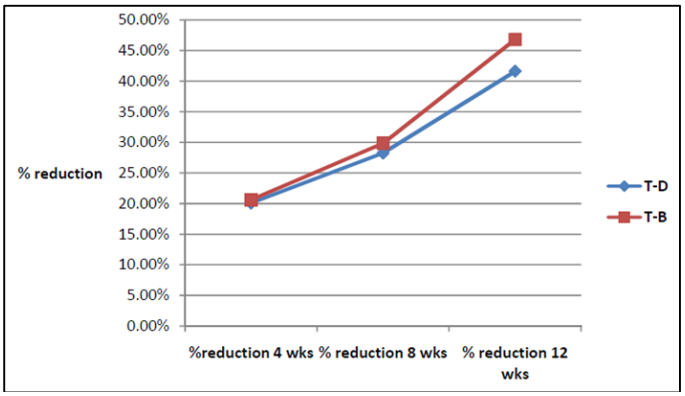

Fig 1: Mean percent reduction in IOP of two treatments at all visits is as follows

Discussion

Glaucoma is the second most common cause of blindness worldwide. Raised IOP is the only risk factor that can be pharmaco- modulated in glaucoma and as per Advanced Glaucoma Intervention Study (AGIS) criteria there was no net visual field progression in a subset of patients in which the IOP is always less than 18 mmHg. [8] Shin *et al*. have done a comparative study between two fixed drug combinations Latanoprost-Timolol versus Dorzolamide-Timolol, and concluded that Latanoprost-Timolol is more efficacious than Dorzolamide-Timolol in the lowering of IOP. [9] Another study was done by Martinez *et al*., showed greater mean IOP reduction with Bimatoprost-Timolol fixed combination compared to Latanoprost-Timolol fixed combination in patients with open-angle glaucoma. [10] Our study results were also similar to R. Jothi *et al*. who has conducted her eight-week study in parts of Tamilnadu. [11]

Conclusion

In this present study, the prevalence of primary open-angle glaucoma increases above age forty. Males are commonly affected than females. There is an influence of family history in primary open-angle glaucoma. Timolol-Bimatoprost producing the greater reduction in mean IOP than Timolol-Dorzolamide at 8 and 12 weeks treatment. Good treatment compliance with minimal adverse effects was found with Timolol-Bimatoprost than Timolol-Dorzolamide. Hence, Timolol+Bimatoprost fixed combination was more efficacious and safe compared to Timolol+Dorzolamide fixed combination in the treatment of primary open-angle glaucoma

Acknlowdgement
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