

Latanoprost Timolol Regime Vs Brimonidine Timolol Regime in Primary Open Angle Glaucoma Uncontrolled with Timolol Alone

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ABSTRACT

A randomized, prospective, interventional comparative study was conducted in 50 patients with primary open angle glaucoma (POAG) or ocular hypertension (OHT) for 13 months. The eyes were categorized as Group A consisting 48 eyes and group B consisting 48 eyes. The purpose of the study was to compare the efficacy and safety of treatment regimens with a combination of 'Latanoprost with Timolol' and 'Brimonidine with Timolol' in patients of primary open angle glaucoma uncontrolled with timolol alone. Patients of group A were given a combination of Latanoprost 0.005% with timolol 0.5% once daily and group B were given a combination of Brimonidine 0.2% with timolol 0.5% twice daily. The outcomes were difference from baseline to month 6 in mean IOP reduction, mean best corrected visual acuity (BCVA), mean vertical cup:disc ratio (CDR), mean average retinal nerve fibre layer (RNFL) thickness, mean average rim area, mean deviation (MD) and pattern standard deviation (PSD). Mean baseline IOP levels in mmHg were 27.58(SD 3.28) in group A and 28.08(SD 3.11) in group B. At month 6, levels were 15.64(SD 1.42) in group A and 17.27(SD 2.35) in group B. Outcome at 6 month in BCVA, CDR, average RNFL and average rim area also showed significant difference between the groups. The adverse events occurred equally, 42 in group A and 44 in group B. The combination of Latanoprost/Timolol given once daily has more efficacy, equal safety and tolerability as compared to the combination of Brimonidine/Timolol given twice daily.

KEY WORDS: brimonidine, latanoprost, primary open angle glaucoma (POAG), timolol

INTRODUCTION:

Glaucoma is a leading cause of irreversible blindness throughout the world. World Health Organization statistics indicate that glaucoma accounts for blindness in 5.1 million persons, or 13.5% of global blindness (behind only cataracts and trachoma at 15.8 million persons, or 41.8% of global blindness, and 5.9 million, or 15.5%, respectively).^[1] Worldwide, it has become the second most common cause of bilateral blindness. Open angle glaucoma and angle closure glaucoma was estimated to affect approximately 66.8 million persons by the year 2000, with 6.7 million experiencing bilateral blindness.^[2]

The term glaucoma refers to a collection of diseases with diverse clinical and histopathologic manifestations characterized by progressive,

distinctive changes in the visual field and the optic nerve. Primary open-angle glaucoma (POAG) is a generally bilateral disease of adult onset characterized by more than 21 mmHg at some stage, glaucomatous optic nerve damage, an open anterior chamber angle, characteristic visual field loss as damage progresses, absence of signs of secondary glaucoma or a non-glaucomatous cause for the optic neuropathy. In general population, the mean IOP is 16 mmHg; two standard deviations on either side of this gives a 'normal' IOP range 11-21 mmHg. It is estimated that 4-7% of the population over the age of 40 years have IOPs >21 mmHg without detectable glaucomatous damage: ocular hypertension (OHT).

Diagnosing POAG requires evaluation of IOP, the anterior chamber angle (by gonioscopy), optic disc, and visual field. In glaucoma, there may be concentric enlargement of the optic cup or preferential superior and inferior cupping with focal notching of the rim of the optic disc. As cupping develops, the

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Figure 1: Glaucomatous cupping of a patient showing raised cup: disc ratio of about 0.6 and nasal shifting of vessels in right eye.

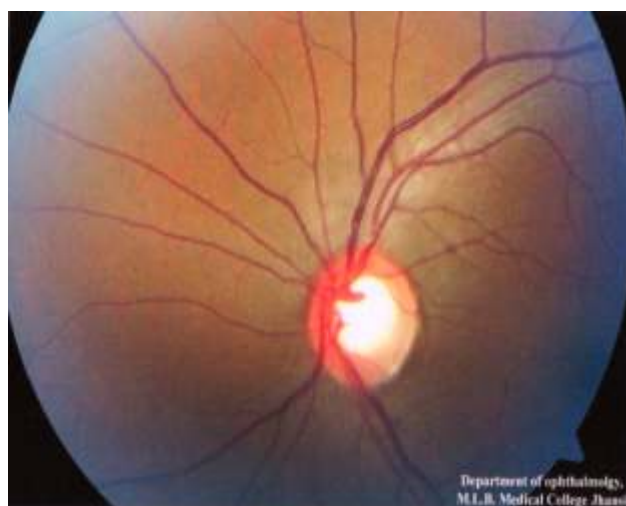


Figure 2: Glaucomatous cupping of a patient showing raised cup: disc ratio of about 0.6 and nasal shifting of vessels in left eye.

retinal vessels on the disc are displaced nasally (Figure 1,2). Glaucomatous field loss involves mainly the central 30 degrees of field (Figure 3,4). The earliest change is baring of the blind spot. Contiguous extension into Bjerrum's area of the visual field at 15 degrees from fixation-produces a Bjerrum scotoma and then an arcuate scotoma. Focal areas of more pronounced loss within Bjerrum's area are known as Seidel scotomas. Double arcuate scotomas-above and below the horizontal meridian-are often accompanied by a nasal step (of Roenne) because of differences in size of the two arcuate defects. Peripheral field loss tends to start in the nasal periphery as a constriction of the isopters. Subsequently, there may be connection to

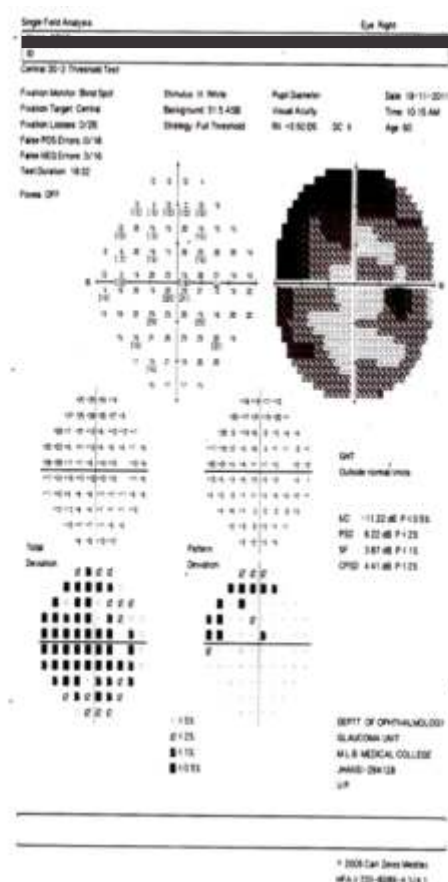


Figure 3: Perimetry report of a patient's right eye showing glaucomatous field defects.

an arcuate defect, producing peripheral breakthrough. The temporal peripheral field and the central 5-10 degrees are affected late in the disease.

Topical hypotensive medication is considered the treatment of choice in the initial management of increased intraocular pressure (IOP) in patients with glaucoma. Target IOP levels are not always achieved with the use of one agent, however, and many patients require combination therapy.^[3,4] Latanoprost/Timolol is a combination drug used in glaucoma, consisting of latanoprost (prostaglandin analogue, increasing the outflow of aqueous fluid from the eyes through the uveal-scleral tract) and timolol (a beta blocker decreasing the production of aqueous fluid). As a class, PG analogues are the most effective topical agents currently available for lowering intraocular pressure (IOP).^[5-8] The OBBs lower IOP through a reduction in aqueous formation. Aqueous formation can decrease by as much as 50%.^[9,10] It is expected that the effects of beta blockers and PGs on IOP reduction

would be additive, and this has been confirmed in clinical studies. In several trials in which latanoprost once daily was added to timolol twice daily, additional IOP reductions of 24% to 37% were achieved.^[11-13] Latanoprost has been FDA approved as a first-line treatment of open-angle glaucoma or ocular hypertension since 2002. A fixed-combination of latanoprost 0.005% and timolol 0.5% is available. There is substantial evidence that the fixed-combination product is more effective than either timolol or latanoprost alone.^[11-16] Fixed combinations of latanoprost and timolol reduce IOP an additional 15% to 25% below a timolol-treatment baseline or a latanoprost-treatment baseline.^[11-16]

Brimonidine/ Timolol is combination of brimonidine (an α_2 adrenergic agonist) and timolol (a β adrenergic blocker), in concentrations of 0.2% and 0.5% respectively. Both substances work by decreasing the synthesis of aqueous humor. Brimonidine reduces IOP in ocular hypertensive patients by reducing aqueous flow (20%) and possibly by increasing uveoscleral outflow.^[17] Brimonidine is the latest alpha agonist to be approved by the FDA for the treatment of glaucoma.

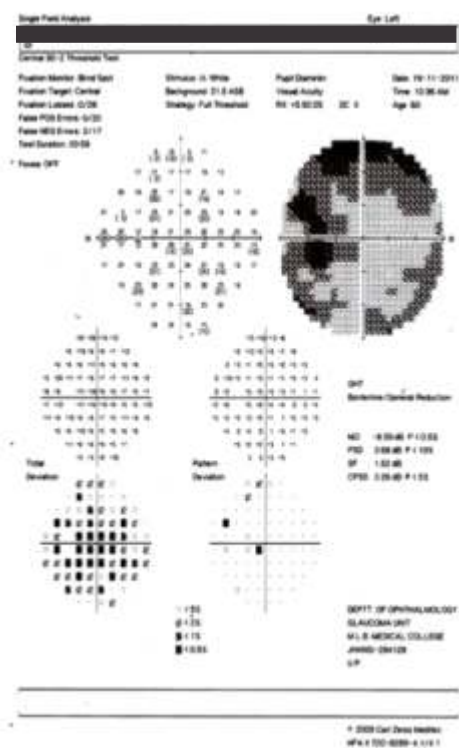


Figure 4: Perimetry report of a patient's left eye showing glaucomatous field defects.

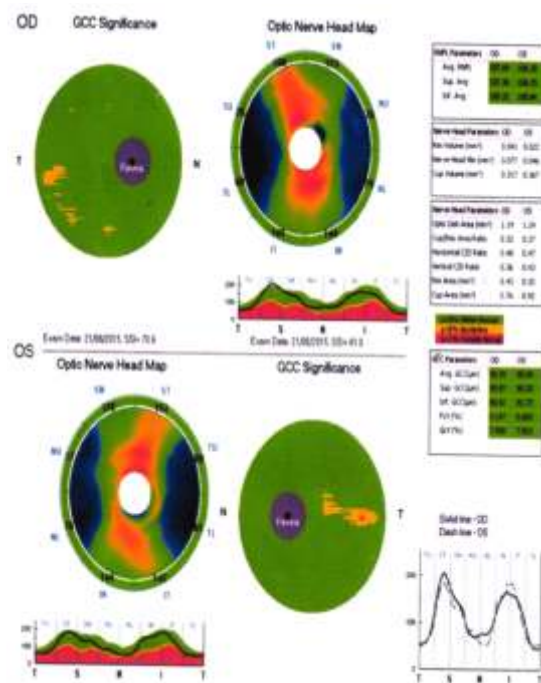


Figure 5 : OCT of a patient.

MATERIALS AND METHODS:

A total of 50 patients of either sex suffering from POAG uncontrolled with timolol alone were evaluated and randomly divided into two groups (96 eyes: 4 patients were uniocular) were included in this study conducted in the Department of Ophthalmology, Maharani Laxmi Bai Medical College, Jhansi, Uttar Pradesh, India over a period of 13 months from February 2014 to February 2015. The procedures followed were in accordance with the ethical standards committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2000. The necessary permission from the Ethical and Research Committee was obtained for the study.

First group 'A' comprising of 25 patients was given a combination of LATANOPROST-TIMOLOL and the second group B of another 25 patients was given a combination of BRIMONIDINE-TIMOLOL. Inclusion criteria was: 18 years of age; Unilateral or bilateral primary open angle glaucoma (POAG), pigmentary glaucoma, or exfoliative glaucoma or ocular hypertension (IOP ≥ 21 mm Hg); At screening, inadequate response to monotherapy or dual therapy (IOP > 16 mm Hg); At baseline, following washout of previous therapy, the patients having: Mean 12:00 PM IOP ≥ 25 mm Hg and an

increase in IOP 3 mm Hg from screening; BCVA 20/80; Able to comply with protocol requirements. The patients having history of one or more of the following were excluded: acute angle closure glaucoma; closed or barely open anterior chamber angle; argon laser trabeculoplasty or any ocular surgery or inflammation or infection within 3 months of screening; ocular filtering surgery; other abnormal ocular conditions; sensitivity to benzalkonium chloride or any other component of drug solutions; a condition in which treatment with a adrenergic receptor antagonist is contraindicated; concurrent use of monamine oxidase (MAO) inhibitors or tricyclic antidepressants (TCA); use of an investigational medication within 1 month before screening; use of systemic medication known to affect IOP unless both patient and dosage were stable for preceding 3 months and no change in dosage expected during study period; pregnancy or lactation. For eligible patients, current ocular hypotensive treatments were suspended with required prebaseline washout periods of 4 weeks for blockers and prostaglandin analogues, 2 weeks for adrenergic agonists, and 5 days for cholinergic agonists and carbonic anhydrase inhibitors.

Fixed drug combinations were used as Latanoprost 0.005% with timolol 0.5% once daily given to patients of group A and Brimonidine 0.2% with timolol 0.5% twice daily given to patients of group B. Eyes that met all inclusion and no exclusion criteria were designated as study eyes. After taking proper consent and without any financial interest a complete general examination is done, a detailed ocular examination was performed in the following sequence. First visual acuity was assessed as per BCVA logMAR chart. Then IOP (mmHg) by indentation tonometer (Schiotz tonometer) was obtained to have baseline documentation on day 1. Slit lamp biomicroscopy and gonioscopy were done. Fundus examination using 78 D/90D was done. Visual fields parameter using 30-2 SITA standard full threshold programme on Humphrey Field analyser perimeter were recorded as mean deviation (MD) and pattern standard deviation (PSD). OCT was analysed for vertical CDR, average RNFL and average rim area (Figure 5). The patients were followed up for IOP (mm Hg) at 12 PM for each eye at 1 week, 1 month, 3 month

and 6 month respectively. And for vertical CDR, average RNFL, average rim area, MD and PSD at 6 month. Ocular findings and adverse events regardless of relation to treatment were monitored throughout. Investigators recorded observed adverse events, as well as those reported spontaneously by patients and those elicited by questioning.

The patient's protocols were recorded in data collection form. Quantitative data were expressed as mean and qualitative variables were expressed using percentages. We applied Student's unpaired 't' test for equal or unequal variances, after calculating the variance of each data groups respectively. The p-value of < 0.05 for one - tailed hypothesis was considered statistically significant to reject the 'null hypothesis'. If the z test value or the observed difference between two means is greater than 2 times of standard error of difference (SED), it is significant at 5% level of significance. All statistical calculation/descriptive analyses (except z test value, that was calculated manually using the formula) were made with the help of data analyses tool of Microsoft Excel 2007.

RESULTS:

The mean age in this study in years was 43.52 in group A and 42.52 in group B (range 20 to 60 years) (Table 1). 16 patients in group A and 18 patients in group B were male, while 9 patients in group A and 7 patients in group B were female (Table 2). 56% patients in the study group were from low socio-economic strata (Table 3).

Thirty seven patients were diagnosed with POAG and 8 patients were having OHT (Table 4). The study groups, along with suspicious glaucomatous cupping, also had other additional suspicious glaucomatous fundus changes such as notching was present in 15.6% cases, bayonetting of vessels in 19.79%, laminar dot sign in 9.37% cases, disc hemorrhage in 7.29% and baring of circumferential blood vessels (BCLV) (Table 5). [The tables shown herein (Table 1 to Table 13) are based on extensive data set a detailed study].

Efficacy:

The mean BCVA (logMAR) of group A increased from baseline values by 3.83%, while the

Table 1: Mean age distribution

Age (yrs)	Group A	Group B	z test	p value
Mean	43.52	42.52	0.4314	0.50
SD	±10.4367	±12.5037		

Table 2: Gender distribution in study groups.

Sex	Total number of patients	Group A (%)	Group B (%)	p value
Male	34 (68%)	16 (32%)	18 (36%)	0.31
Female	16 (32%)	9 (18%)	7 (14%)	0.26

Table 3: Socio-economic status of the study groups

Socioeconomic status	Number of patients	Percentage
High	4	8%
Medium	18	36%
Low	28	56%
Total	50	100%

Table 4: Distribution of specific diagnosis included in both groups.

Primary diagnosis	Total no of patients	Group A	Group B	p value
Primary open angle glaucoma (POAG)	37	18	19	0.50
Ocular hypertension (OHT)	8	4	4	
Pigmentary glaucoma	3	2	1	
Exfoliative glaucoma	2	1	1	
Total	50	25	25	

mean BCVA (logMAR) of group B increased from baseline values by 20.77 % after 6 months of treatment (Table 6, 7). Hence, group A showed much less deterioration of best corrected visual acuity from baseline as compared to group B. The p value was 0.0097 indicating that there was a significant difference in mean baseline BCVA in the two groups. The mean IOP was consecutively reduced at each follow up in both the groups (Table 8, Graph 1). The mean IOP at 1 week was reduced from mean baseline IOP by about 10.67 % in group A and 12.79 % in group B. The mean IOP at 1 month was reduced from mean baseline IOP by about 18.13 % in group A and 19.16 %

in group B. The mean IOP at 3 months was reduced from mean baseline IOP by about 34.37 % in group A and 32.48 % in group B. The mean IOP at 6 months was reduced from mean baseline IOP by about 43.3 % in group A and 38.5 % in group B, with a p value of 0.00004244 (<0.05) showing a high statistically significant difference. In this study, all eyes in group A versus 81.25% of Group B treated eyes achieved $\geq 30\%$ IOP reduction after 6 months, a magnitude likely to be clinically beneficial. Some clinicians prefer to set a target IOP level for their patients, and IOPs ≤ 18 mm Hg have been associated with slowed disease progression in patients with ocular hypertension and glaucoma.^[18,19] Herein, all the eyes in the Latanoprost/Timolol treated group A achieved IOP levels of ≤ 18 mm Hg compared with the Brimonidine/Timolol treated group B (70.88%). Also 75% of the eyes in group A achieved IOP levels of ≤ 16 mm Hg compared with group B (41.66%).

On clinical evaluation of vertical CDR, the mean CDR increased from baseline in group A by 2.519% and in group B by 14.08%, with a significant p value of 0.019 (>0.05). The results showed less changes in mean CDR at 6 months from baseline in group A as compared to group B (Table 9, Graph 2). However, the vertical CDR in OCT showed that the mean CDR decreased from baseline in group A by 3.34% and increased from baseline in group B by 2.39%, with a significant p value of 0.0447 (Table 10, Graph 3).

The mean RNFL (μ m) in OCT at 6 months was found to increase from baseline in group A by 2.887(2.93%) and decrease in group B by 4.158(4.22%) with a statistically significant p value of 0.0475 (Table 11, Graph 4). Follow up Mean Rim Area(mm^2) at 6 months was found to increase from baseline in group A by 0.0341(3.37%) and decrease in group B by 0.0535(5.42%) with a statistically significant p value of 0.0204 (Table 12, Graph 5). The follow up MD at 6 months showed variable results in both the study groups. MD at 6 months in group A decreased from baseline by 0.1122 (2.42%) while in group B increased from baseline by 0.3678 (7.348%). The follow up PSD at 6 months also showed variable results in both the study groups. PSD at 6 months in group A increased from baseline by 0.30295 (7.94%)

Table 5: Other suspicious glaucomatous signs found in study groups.

	Total no. of eye	Group A	Group B	p value
Notching	15 (15.62%)	9 (18.75%)	6 (12.5%)	0.50
Bayonetting	19 (19.79%)	8 (16.66%)	11 (22.91%)	
Laminar Dot sign	9 (9.37%)	5 (10.41%)	4 (8.33%)	
Disc Hemorrhage	7 (7.29%)	3 (6.25%)	4 (8.33%)	
BCLV	8 (8.33%)	4 (8.33%)	4 (8.33%)	

Table 6: Baseline characteristics

Variables	Group A	Group B	p value
Mean age (years)	43.52	42.52	0.50
SD	±10.4367	±12.5037	
Gender			
Male	16	18	0.31
Female	9	7	0.26
Baseline BCVA (log MAR)	0.49117	0.51240	0.20
	±0.13122	±0.11309	
Mean IOP (mm Hg)	27.58	28.08	0.22
	±3.2824	±3.118	
Clinically assessed mean CDR (cup : disc ratio)	0.516	0.504	0.29
	±0.0947	±0.1223	
Optical Coherence tomography (OCT)			
Baseline Mean vertical CDR in OCT	0.5450	0.5520	0.37
	±0.0889	±0.0917	
Mean baseline RNFL (µm) in OCT	98.07	98.64	0.43
	±14.71	±16.18	
Mean baseline rim area (mm ²) in OCT	1.0106	0.9875	0.30
	±0.1967	±0.2314	
Visual field test parameter			
Mean Deviation (MD)	-4.6398	-5.005	0.26
	±2.8278	±2.8101	
Pattern Standard Deviation (PSD)	3.8133	4.409	0.12
	±2.7160	±2.8786	

while in group B decreased from baseline by 0.032188 (7.87%) (Table 6, 7).

Safety:

There was no statistical difference in the total number of adverse events, or for any individual

adverse events, between the two treatment groups. 42 events were observed in the patients of group A and 44 events were observed in the patients of group B during the study duration (table 13). Group B had higher rates of allergic conjunctivitis (12% versus no event in group A), blepharitis (12% versus 4% in group A), dry

Table 7: Follow up characteristics of two groups

Variables		Group A	Group B	p value
BCVA (logMAR)		0.50998	0.61088	
	6 months	± 0.19278	± 0.22190	0.0097
		22.64	24.66	
	1 week	± 2.1018	± 2.3015	0.4779
Mean IOP (mm Hg)		22.58	22.70	
	1 month	± 2.8197	± 2.4810	0.4119
		18.10	18.96	
	3 months	± 2.7117	± 2.8134	0.0671
Mean CDR (cup: disc ratio) SD		15.64	17.27	
	6 months	± 1.4249	± 2.3570	<0.05
		0.529	0.575	
	6 months	± 0.0966	± 0.1157	0.019
Optical coherence tomography				
Follow up mean vertical CDR in OCT		0.5268	0.5652	
	6 months	± 0.1244	± 0.1245	0.0447
Follow up mean RNFL (μm) in OCT		100.95	94.48	
	6 months	± 19.53	± 18.02	0.0475
Follow up mean baseline rim area (mm^2) in OCT		1.0447	0.9339	
	6 months	± 0.2355	± 0.2854	0.0204
Follow up Visual field test parameter				
Mean Deviation (MD)		-4.6398	-5.005	
	6 months	± 2.8278	± 2.8101	0.2632
Pattern Standard Deviation (PSD)		3.8133	4.409	
	6 months	± 2.7160	± 2.8786	0.1171

mouth (12% versus no event in group A) and dry eye (20% versus 8% in group A. While group A had higher rates of eyelash changes (16% versus 4% in group B), iris hyperpigmentation (20% versus no event in group B) and cystoid macular edema/CME (16% versus no event of group B).

DISCUSSION:

With regional burden of blindness (RBB) being highest for India (23.5% of global blindness)^[20], it is imperative to find measures to detect the disease in early stages before it starts to cause visual morbidity.

This study included a total of 50 patients with 34 males (68%) and 16 females (32%). The results were consistent with the finding of Gordon, Mae O, et al. (2002) 'The Ocular Hypertension Treatment Study'^[21], Leske, M. Cristina, et al. (1994) 'The Barbados Eye Study'^[22] and Rudnicka, Alicja R., et al (2006)^[23]. who found that men were 1.37 times more likely to have open angle glaucoma than women but the subject of sex prevalence of POAG has always been controversial. Majority of the patients in the present study were found to be above the age of 40 years (60%). Majority of the subjects (56%) were from low

Table 8: Comparison of follow up mean IOP between the two groups.

IOP (mm Hg)		Group A	Group B	z test	p value
Baseline	mean	27.58	28.08	0.7579	0.22
	SD	±3.2824	±3.118		
1 week	mean	22.64	24.66	0.0439	0.48
	SD	±2.1018	±2.3015		
1 month	mean	22.579	22.70	0.1880	0.41
	SD	±2.8197	±2.4810		
3 months	mean	18.10	18.96	0.2123	0.07
	SD	±2.7117	±2.8134		
6 months	mean	15.64	17.27	4.057	0.00
	SD	±1.4249	±2.3570		

socio-economic strata, which is in resonance with the study conducted by King AJ et al(2000)^[24], which concluded that low socio economic background was indeed a risk factor for development of glaucoma despite universal health care.

Achieving and maintaining low target IOP minimizes the risk of glaucomatous progression and vision loss.^[25,26] In the present study, in the initial 1 month of treatment, group B showed more reduction in mean IOP from baseline in terms of percentage. But there was no statistically significant difference between the two groups at this point. While on further follow up at 3 months and 6 months respectively, group A showed much more further reduction in IOP from baseline in terms of percentage as compared to group B (table 8, graph 1). This study was powered to detect a treatment difference of 1.63 mm Hg in the change of IOP from baseline to 6 months using an unpaired *t* test ($p < 0.00004244$), supporting the conclusion that once daily Latanoprost with Timolol combination more effectively reduces IOP levels than twice daily Brimonidine with Timolol combination. Prospective, double masked study by Kampik A, Arias-Puente A, O'Brart DPS, et al^[27] and by Stewart WC, Day DG, Stewart JA, et al^[28] have shown that once daily latanoprost is superior to twice daily brimonidine when used as monotherapy, and one retrospective study by Stewart WC, Sharpe ED, Day

DG, et al has found latanoprost to be superior to brimonidine when used adjunctively to timolol.^[29] Findings of the Early Manifest Glaucoma Trial have shown that the magnitude of IOP reduction is a major factor influencing disease progression.^[30] Progression risk was estimated to decrease by approximately 10% with each millimetre of mercury of IOP reduction. An IOP reduction of 30% has been shown to slow the rate of visual field progression among normotensive glaucoma patients^[31] and it has been confirmed in ocular hypertension that even a more modest 20% reduction is an acceptable response to treatment.^[32]

In this study, optic disc morphology showed a significant change between both the treatment groups. Although published articles about the change in optic disc morphology using OCT in subjects treated with

Table 9: Comparison of follow up cup: disc ratio (CDR) assessed clinically after 6 months in both groups.

	Group A	Group B	z test	p value
Baseline	0.516	0.504	0.5820	0.29
6 months	±0.0947	±0.1223	2.093	0.02
	0.529	0.575		
Increased from Baseline	±0.0966	±0.1157	0.013	0.071
	0.013	0.071		

Table 10: Follow up vertical CDR (cup: disc ratio) of two groups in OCT at 6 months.

	Group A	Group B	z test	p value
Baseline	0.5450 ±0.0889	0.5520 ±0.10917	0.3108	0.37
6 months	0.5268 ±0.1244	0.5652 ±0.1245	1.4957	0.04
Difference from Baseline	0.0182 (Decreased by)	0.0132 (Increased by)		

Table 11: Follow up Mean Retinal Nerve Fibre Layer (RNFL) in μm thickness of two groups in OCT at 6 months

Mean RNFL Thickness (μm)	Group A	Group B	z test	p value
Baseline	98.07 ±14.71	98.64 ±16.18	0.1787	0.43
6 months	100.95 ±19.53	94.48 ±18.02	1.6691	0.05
Difference from baseline	2.887 (Increased by)	4.158 (Decreased by)		

combination drugs could not be found, a retrospective study by Güliz Fatma YAVA *, Tuncay KÜSBEC , Onur POLAT, Mahmut KARADA , Sıtkı Samet ERM , Ümit Übeyt NAN,^[33] showed no significant changes in optic disc morphology in individual groups treated with Latanoprost/Timolol and Brimonidine/Timolol respectively. But there are some reports using the HRT (Heidelberg Retinal Tomograph) or scanning laser polarimetry. The HRT revealed optic disc changes in 14.3% of subjects using Latanoprost/Timolol, which was not statistically significant after logistic regression analysis^[34]. However, the results in OCT in the present study show that in group A the Latanoprost/ Timolol combination seemed to have a beneficial effect in halting the optic disc morphology changes at 6 months as compared to group B treated by Brimonidine/Timolol combination.

Table 12: Follow up mean Rim Area (mm^2) of two groups in OCT at 6 months

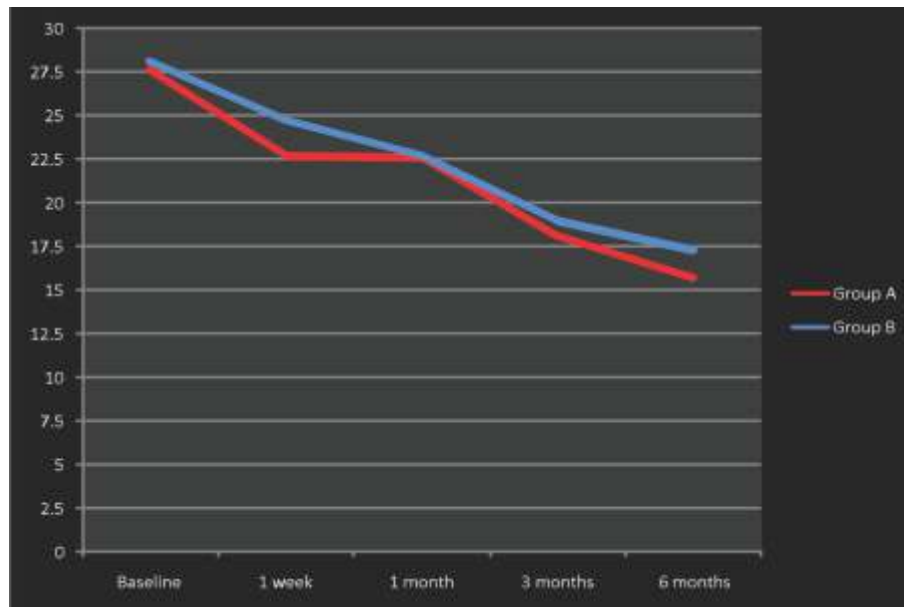
Mean RNFL Thickness (μm)	Group A	Group B	z test	p value
Baseline	1.0106 ±0.1967	0.9875 ±0.2314	0.6433	0.30
6 months	1.0447 ±0.2355	0.9339 ±0.2854	1.8443	0.02
Difference from baseline	0.0341 (Increased by)	0.0535 (Decreased by)		

Table 13: Distribution of various side effects / adverse events seen in patients of both groups.

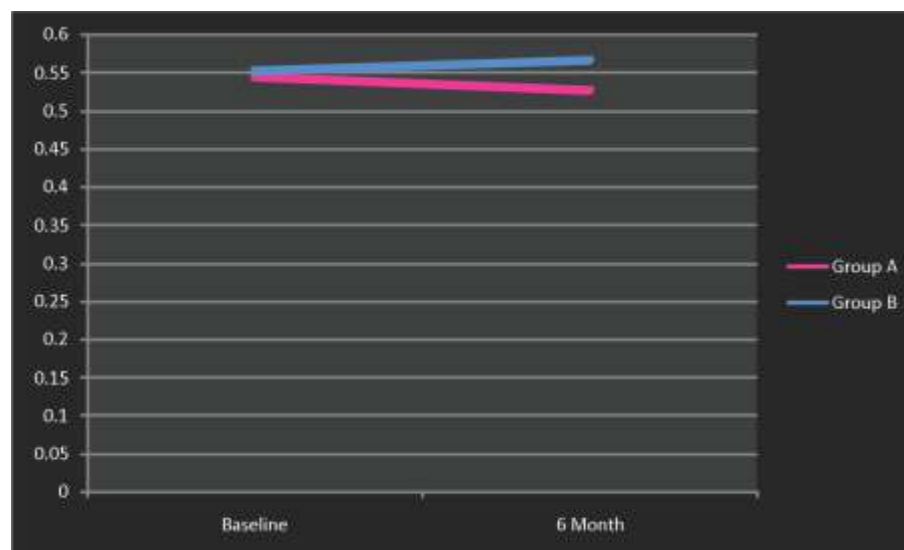
Side effect	Total no of adverse events	Group A	Group B	p value
Burning	7	4	3	0.42
Conjunctival hyperaemia	6	2	4	
Allergic conjunctivitis	3	0	3	
Ocular itching	11	5	6	
Watering	4	2	2	
Dry eye	7	2	5	
Eyelid laxity	3	2	1	
Blurred vision	6	3	3	
Floaters	5	2	3	
Photophobia	4	2	2	
Eyelash changes	5	4	1	
Iris hyper pigmentation	5	5	0	
Cystoid macular oedema (CME)	4	4	0	
Blepharitis	4	1	3	
Diplopia	4	2	2	
Soreness	3	1	2	
Dry mouth	3	0	3	
Sinus allergies	2	1	1	
Total	86	42	44	

In subjects with early glaucoma, evaluation of the RNFL is important for evaluating glaucomatous

Graph 1: Comparison of follow up mean IOP between the two groups.



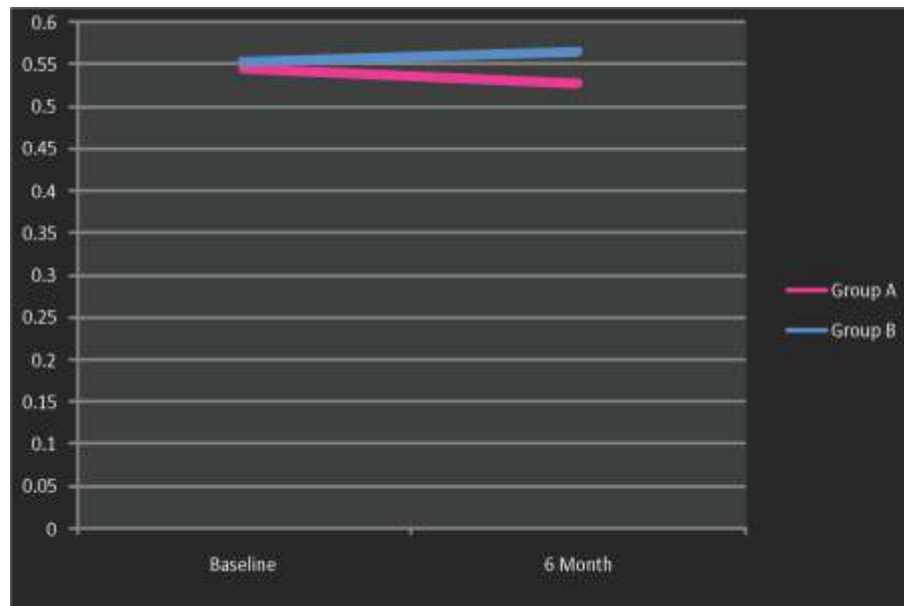
Graph 2: Comparison of follow up cup: disc ratio (CDR) assessed clinically after 6 months in both group.



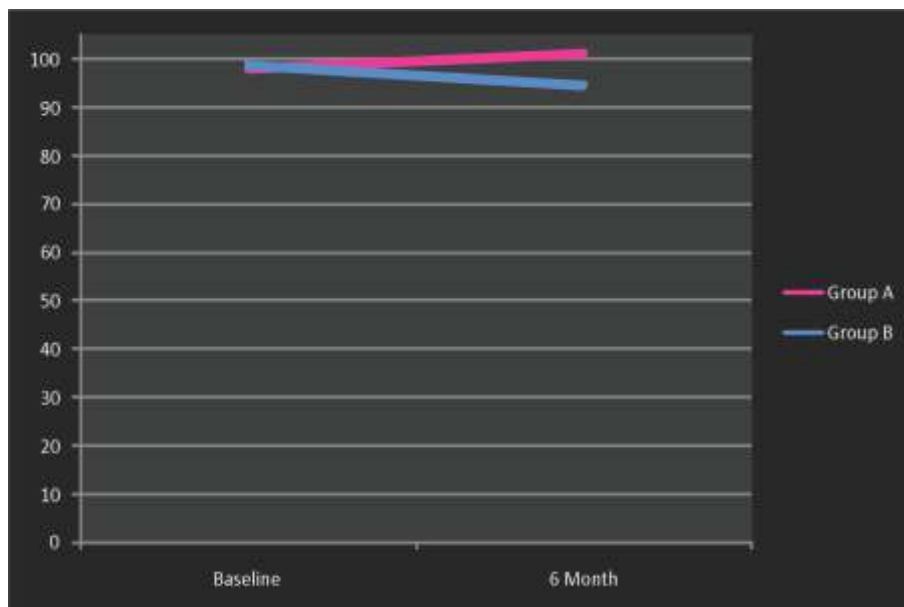
ganglion cell loss. Kanamori et al.^[35] showed that the RNFL decreased in glaucomatous eyes, with or without early visual field defects. This showed that Latanoprost/Timolol combination in group A had favourable effects in preventing the progression of RNFL thinning as compared to Brimonidine/Timolol combination in group B. The combination of Latanoprost/Timolol in group A also depicted favourable results in increasing the mean rim area as compared to the combination of Brimonidine/Timolol given to the patients of group B. Visual field did not show any change during treatment in either

group. This is supported by a retrospective study by Güliz Fatma YAVA *, Tuncay KÜSBEC, Onur POLAT, Mahmut KARADA, Sıtkı Samet ERM, Ümit Übeyt NAN^[33] who found that both combinations in group A and group B were effective in preventing progression of glaucomatous visual field damage. There was no change in MD, PSD, SF, or CPSD in treatment groups compared to the baseline. Each 1 mmHg rise in IOP during a median follow-up time of 5.3 years has been shown to be associated with a 19% increased risk of visual field progression^[36]. This can explain why the present study observed no

Graph 3: Follow up vertical CDR (cup: disc ratio) of two groups in OCT at 6 months.



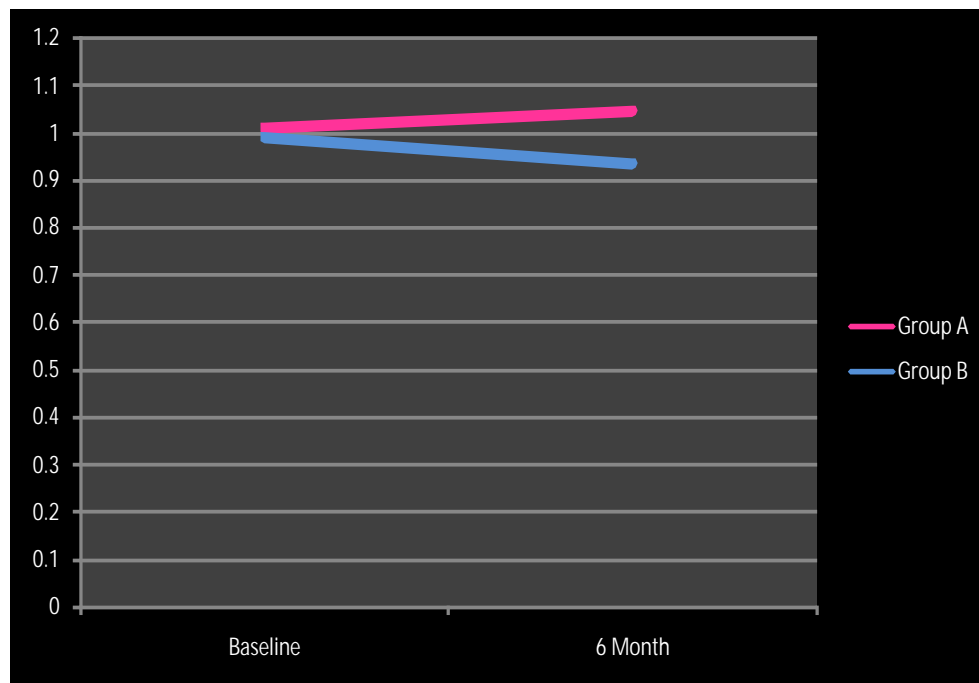
Graph 4: Follow up Mean Retinal Nerve Fibre Layer (RNFL) in μm thickness of two groups in OCT at 6 months.



changes in visual fields in the study groups. Nevertheless, progression of visual field disorder in glaucoma is usually slow.

In group A, prominent side effects were 5 events of iris hyperpigmentation, 4 events of Cystoid macular oedema (CME) and 4 events of eyelash changes. In group B, prominent side effect were 5 events of dry eye, 3 events of blepharitis and 3 events of dry mouth. Rest of the adverse events occurred equally in both the study groups. The patients of group

A had a slightly lower incidence of treatment related adverse events (68%) as compared to group B (76%). Systemic adverse effects in both the groups were not present, this difference to other study (Craven et al 2005; Goni et al 2005; Sherwood et al 2006)^[14-16] in systemic side effect profile may be explained by selection bias, as patients with adverse events with beta-blocker therapy, previous poor response to beta-blocker or systemic contraindications to the medication were excluded.

Graph 5: Follow up mean Rim Area (mm²) of two groups in OCT at 6 months

The only problem with Latanoprost/Timolol combination was storage problem. It is recommended to store unopened bottles in the refrigerator, between 36 and 46 degrees F (2 and 8 degrees C) and are not to be frozen. Opened bottles may be stored at room temperature, up to 77 degrees F (25 degrees C), for up to 6 weeks. In terms of cost, Latanoprost/Timolol combination is costlier than Brimonidine/Timolol combination. But, keeping in mind the once daily dosage of Latanoprost/Timolol combination as compared to twice daily dosage of Brimonidine/Timolol combination, the overall financial burden of both the groups' drugs was comparable.

CONCLUSION:

It is concluded that combination of Latanoprost/ Timolol has more efficacy than the combination of Brimonidine/Timolol in reducing IOP, reducing the worsening of visual acuity and glaucomatous optic nerve defects. However, long term studies are needed to be conducted involving considerations for visual field parameter changes in Perimetry and optic nerve changes in spectralis OCT. Meanwhile, the combination of Latanoprost/ Timolol has been observed to have equal safety and tolerability but higher treatment cost to the combination of Brimonidine/Timolol.

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