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To Compare The Short Term Effects Of Adding Latanoprost To Timolol Regime Versus Timolol In Patients Of Primary Open Angle Glaucoma

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Abstract *:*
Purpose: *To compare the efficacy and safety of treatment regimens with a combination of Latanoprost with Timolol versus Timolol in patients of primary open angle glaucoma.*
Methods: *This 12 months**,** randomized prospective clinical trial consisted of 96 eyes of 50 patients with primary open angle glaucoma(POAG) or ocular hypertension(OHT), categorised as Group A consisting 48 eyes and group B consisting 48 eyes. Patients of group A were given a Latanoprost 0.005% with timolol 0.5% once daily and group B were given timolol 0.5% twice daily. The difference from baseline to month 6 in mean IOP reduction, mean best corrected visual acquity(BCVA), mean vertical cup:disc ratio(CDR), mean average retinal nerve fibre layer(RNFL) were noted.*
Results: *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 17.41(SD 2.35) in group B. Following outcomes at 6 month also showed significant difference between two groups: BCVA, CDR and average RNFL. The adverse events occurred equally, 52 in group A and 46 in group B.*
Conclusion: *The combination of Latanoprost/Timolol given once daily has more efficacy, equal safety and tolerability as compared to Timolol given twice daily.*
Keywords: *open angle glaucoma, timolol, latanoprost*

I. Introduction

Glaucoma is a leading cause of irreversible blindness throughout the world. World Health Organization statistics, published in 1995, 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:

- An IOP >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 the 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).

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] The OBBs lower IOP through a reduction in aqueous formation. Aqueous formation can decrease by as much as 50%.[6,7] 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.[8-10] 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.[8-12]. Fixed combinations of latanoprost and timolol reduce IOP an additional 15% to 25% below a timolol-treatment baseline or a latanoprost- treatment baseline.[8-12]

II. Materials And Methods

A total of 96 eyes of 50 patients (4 patients were uniocular) attending the OPD, were included in this study conducted in our institute over a period of 12 months from February 2014 to January 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.

Patient selection:

Patient selection criteria are summarised as:

Inclusion criteria:

- ≥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 :

1. Mean 12:00 PM IOP ≥25 mm Hg and an increase in IOP ≥3 mm Hg from screening;
2. BCVA ≥20/80;
3. Able to comply with protocol requirements

Exclusion criteria:

The patients having history of one or more of the following ;

- 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 β 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.

Study Protocol:

A total of 50 patients of either sex suffering from POAG were evaluated and randomly divided into two groups. 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 TIMOLOL. For eligible patients, current ocular hypotensive treatments were suspended with required prebaseline washout periods of 4 weeks for β blockers and prostaglandin analogues, 2 weeks for adrenergic agonists, and 5 days for cholinergic agonists and carbonic anhydrase inhibitors. Fixed drug combination was used as Latanoprost 0.005% with timolol 0.5% once daily given to patients of group A while group B patients were given timolol 0.5% twice daily . 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 acquity was assessed as per BCVA logMAR chart. Then IOP(Intraocular Pressure in 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. OCT was analysed for vertical CDR and average RNFL .The patients were followed up for IOP(mm Hg) at 12 PM for each eye at 3 month and 6 month respectively. And for vertical CDR,and average RNFL at 6 months .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.

Statistical Analysis:

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 calculations/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. All analysis were based on extensive data included in the research .

III. Results

The mean age in this study in years was(range 20 to 60 years) 43.52 in group A and 42.52 in group B (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). Overall 37 patients were diagnosed with POAG and 8 patients were having OHT (Table 4).

Efficacy:

The mean BCVA (logMAR) of group A increased from baseline values by 3.83% while the mean BCVA (logMAR) of group B increased from baseline values by 20.01 % after 6 months of treatment (Table 5, 6). So group A showed much less deterioration of best corrected visual acquity from baseline as compared to group B. The p value was 0.009(<0.05) ,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 7, Fig. 1). The mean IOP at 3 months was reduced from mean baseline IOP by about 34.37 % in group A and 31.98% in group B. The mean IOP at 6 months was reduced from mean baseline IOP by about 43.3 % in group A and 38.1 % in group B, with a p value of 0.00004 (<0.05), showing a high statistically significant difference.

In this study, all eyes in group A versus 76.25% of Group B treated eyes achieved $\geqslant$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 $\leqslant$18 mm Hg have been associated with slowed disease progression in patients with ocular hypertension and glaucoma.[13,14] Herein, all the eyes in the Latanoprost/Timolol treated group A achieved IOP levels of $\leqslant$18 mm Hg compared with the Brimonidine/Timolol treated group B (67.56%). Also 75% of the eyes in group A achieved IOP levels of $\leqslant$16 mm Hg compared with group B (38.23%).

On evaluation of 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 2.66%, with a significant p value of 0.04 (Table 8, Fig. 2).

The mean RNFL (µm) 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 0.04 (Table 9, Fig.3).

Safety:

There was no statistical difference in the total number of adverse events, or for any individual adverse events, between the two treatment groups. 52 events were observed in the patients of group A and 46 events were observed in the patients of group B during the study duration (Table 10). Group B had higher rates of allergic conjunctivitis (12% versus no event in group A), blepharitis (12% versus 4% in group A), dry 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). Conjunctival hyperaemia compared with baseline was especially seen in the group A treatment group on day 2(12 events). On day 7, conjunctival hyperaemia increased slightly compared with day 2, being more pronounced on day 9. No changes in hyperaemia were observed with timolol(6 events). The difference in hyperaemia between the two groups was, however, not statistically significant on days 2 and 7 ($p>0.05$).

IV. Discussion

Glaucoma is a leading cause of irreversible blindness throughout the world and the second leading cause of world blindness. It accounts for 15% of global blindness.The regional burden of blindness (RBB) is highest for India (23.5% of global blindness).[15] With such prevalence rates it is imperative for us 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"[16], Leske, M. Cristina, et al. (1994) "The Barbados Eye Study"[17] and Rudnicka, Alicja R., et al (2006)[18] 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 our study were found to be above the age of 40 years (60%). Majority of our subjects (56%) were from low socio-economic strata which is in accordance to study conducted by King AJ et al(2000)[19] who concluded that low socio economic background was indeed a risk factor for development of glaucoma despite universal health care.Achieving and maintaining a low target IOP minimizes the risk of glaucomatous progression and vision loss.[20,21] In this study, on 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 1, Fig. 1). This study was powered to detect a treatment difference of 1.26 mm Hg in the change of IOP from baseline to 6 months using an unpaired- t test ($p<0.05$), supporting the conclusion that once daily Latanoprost with Timolol combination more effectively reduces IOP levels than twice daily Timolol alone. Findings of the Early Manifest Glaucoma Trial have shown that the magnitude of IOP reduction is a major factor influencing disease progression.[22] 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[23] and it has been confirmed in ocular hypertension that even a more modest 20% reduction is an acceptable response to treatment.

In this study, optic disc morphology showed a significant change between both the treatment groups. Although we could not find any articles about the change in optic disc morphology using OCT in subjects treated with combination drugs, a retrospective study by Güliz Fatma YAVAŞ*, Tuncay KÜSBECİ, Onur POLAT, Mahmut KARADAŞ, Sıtkı Samet ERMİŞ, Ümit Übeyt İNAN,[24] 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[25]. However the results in OCT in this study showed 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 Timolol .

In subjects with early glaucoma, evaluation of the RNFL is important for evaluating glaucomatous ganglion cell loss. Kanamori et al.[26] 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 Timolol in group B. n 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. 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)[11,12] 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.

V. Figures And Tables

Table 1: Mean Age Distribution

Age (yrs)	Group A	Group B	z test	p value
Mean	43.52	42.52	0.43	0.50
SD	±10.44	±12.50		

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%)	0.30
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.

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

Table 5: Baseline Characteristics

Variables	Group A	Group B	p value
Baseline BCVA (log MAR)	0.49117 ±0.13	0.51240 ±0.11	0.20
Mean IOP (mm Hg)	27.58 ±3.28	28.08 ±3.11	0.22
Optical Coherence tomography (OCT)			
Baseline Mean vertical CDR in OCT	0.5450 ±0.09	0.5520 ±0.09	0.37
Mean baseline RNFL (µm) in OCT	98.07 ±14.71	98.64 ±16.18	0.43

Table 6: Follow Up Characteristics Of Two Groups

Variables		Group A	Group B	p value
BCVA (logMAR)	6 months	0.50998 ±0.19	0.6149 ±0.22	0.01
Mean IOP (mm Hg)	3 months	18.10 ±2.71	19.10 ±2.81	0.07
	6 months	15.64 ±1.42	17.41 ±2.35	0.00004
Optical coherence tomography				
Follow up mean vertical CDR in OCT	6 months	0.5268 ±0.12	0.5667 ±0.12	0.04
Follow up mean RNFL (µm) in OCT	6 months	100.95 ±19.53	94.54 ±18.02	0.04

Table 7: 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	0.76	0.22
	SD	±3.28	±3.11		
3 months	mean	18.10	19.10	0.21	0.07
	SD	±2.71	±2.81		
6 months	mean	15.64	17.41	4.05	0.00004
	SD	±1.42	±2.35		

Table 8: 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 ±0.09	0.5520 ±0.11	0.31	0.37
6 months	0.5268 ±0.12	0.5667 ±0.12	1.49	0.04
Difference from Baseline	0.0182 (Decreased by)	0.0147 (Increased by)		

Table 9: 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	0.18	0.43
6 months	100.95 ±19.53	94.54 ±18.02	1.67	0.04
Difference from baseline	2.887 (Increased by)	4.10 (Decreased by)		

Table 10: Distribution Of Various Side Effects / Adverse Events Seen In Patients Of Both Groups

S.no.	Side effect	Total no of adverse events	Group A	Group B	p value
1.	Burning	7	4	3	0.42
2.	Conjunctival hyperaemia	18	12	6	
3.	Allergic conjunctivitis	3	0	3	
4.	Ocular itching	11	5	6	
5.	Watering	4	2	2	
6.	Dry eye	7	2	5	
7.	Eyelid laxity	3	2	1	
8.	Blurred vision	6	3	3	
9.	Floaters	5	2	3	
10.	Photophobia	4	2	2	
11.	Eyelash changes	5	4	1	
12.	Iris hyper pigmentation	5	5	0	
13.	Cystoid macular oedema (CME)	4	4	0	
14.	Blepharitis	4	1	3	
15.	Diplopia	4	2	2	
16.	Soreness	3	1	2	
17.	Dry mouth	3	0	3	
18.	Sinus allergies	2	1	1	
	Total	98	52	46	

Figure 1: Comparison Of Follow Up Mean IOP Between The Two Groups.

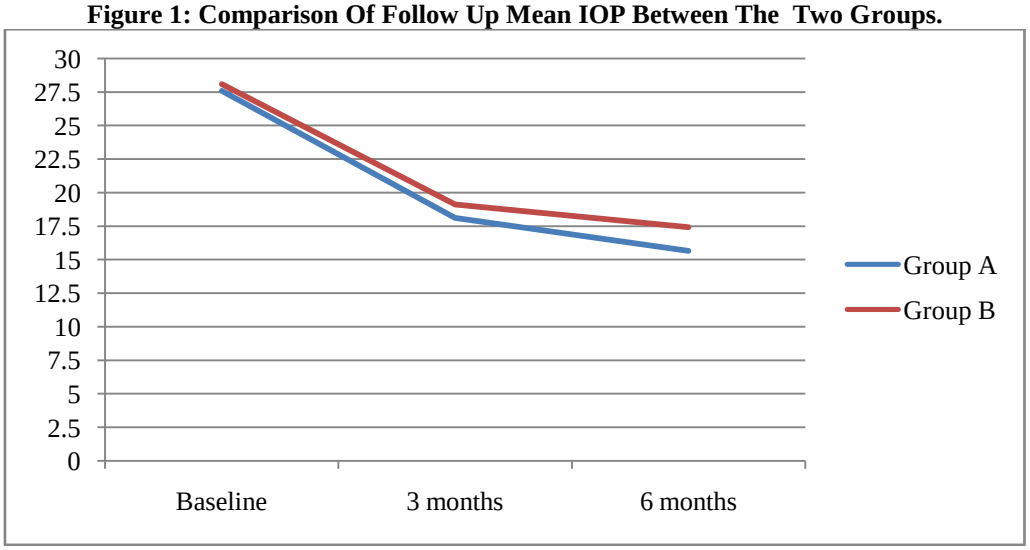


Figure 2: Follow Up Vertical CDR (Cup: Disc ratio) Of Two Groups In OCT At 6 Months.

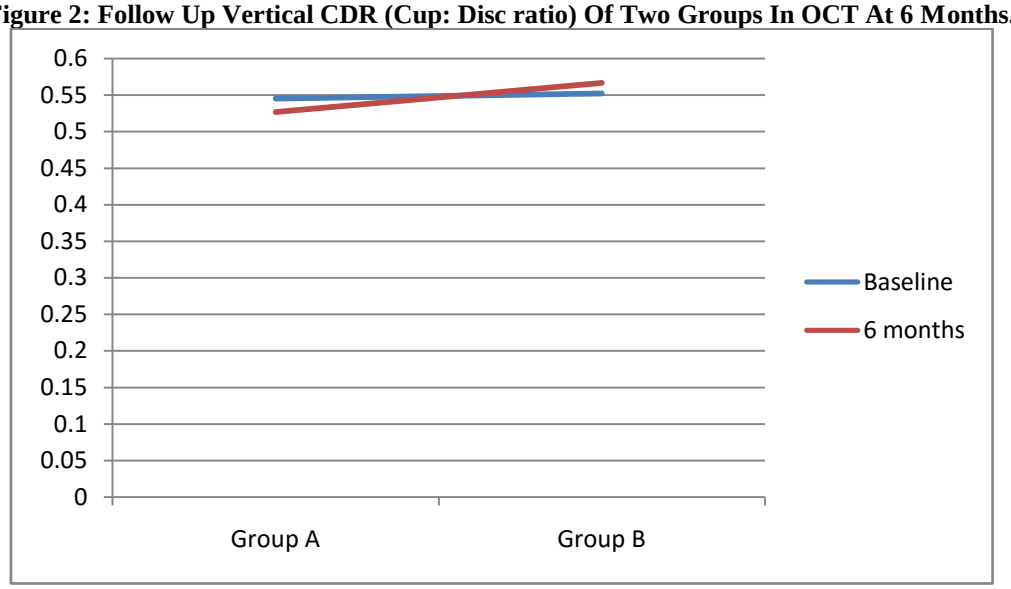
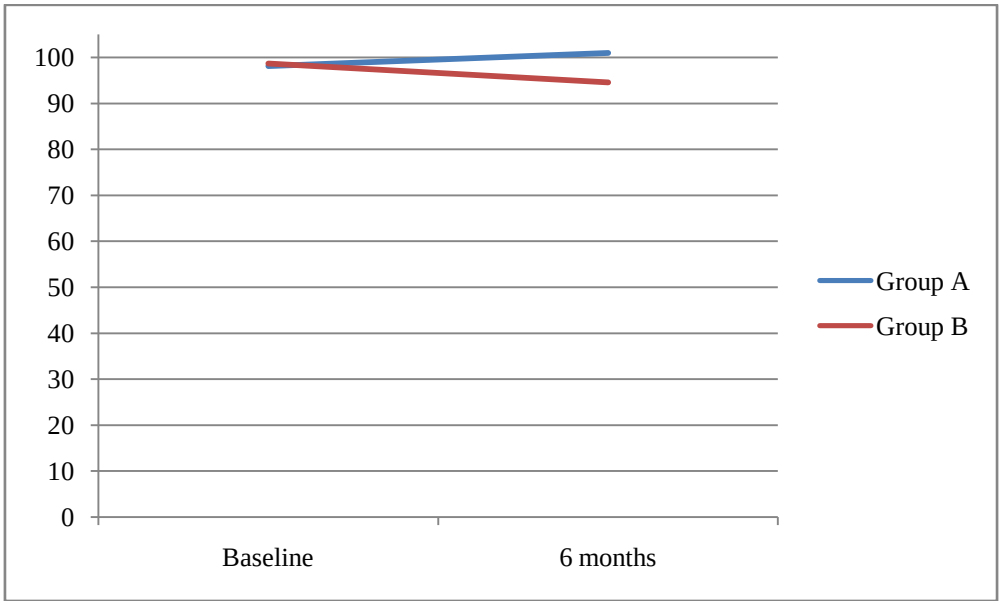


Figure 3: Follow Up Mean Retinal Nerve Fibre Layer (RNFL) In µm Thickness Of Two Groups In OCT At 6 Months.



VI. Conclusion

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). Do not freeze. 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 has somehow more cost profile than Timolol . But the greater efficacy with the fixed combination observed in this study, compared to controlled clinical trials, may have resulted from better compliance. Potentially the once daily dosing, from one bottle, within the experience trial may have allowed for improved pressure control that was not observable in previous well controlled clinical studies. Compact portability, lower cost and comparable reliability made the Schiotz tonometer a viable option for IOP screening in our study. Since the Schiotz tonometer does not measure pressure directly, conversion tables, supplied with the instrument, are used to translate scale readings into estimates of intra-ocular pressure. Two conversion tables are available, published in 1948 and 1955. Studies have shown that the 1948 table more closely approximates pressures obtained with Goldmann applanation tonometry. The Schiotz tonometer is capable of providing measurements accurate enough to screen for a disease that has a long latency period before producing symptoms. The instrument is relatively inexpensive, competency can be gained with a minimum of effort, and it is acceptable to most patients[27].

In this short term study, we concluded that the combination of Latanoprost/Timolol given to the patients of group A has more efficacy than the combination Timolol given to the patients of group B in reducing IOP, reducing the worsening of visual acquity 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 given to the patients of group A has equal safety and tolerability but more cost to Timolol given to the patients of group B.

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