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A COMPARATIVE STUDY OF EFFICACY WITH FIXED DOSE COMBINATION OF LATANOPROST/ TIMOLOL VERSUS BRINZOLAMIDE/ BRIMONIDINE IN PRIMARY OPEN ANGLE GLAUCOMA

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ABSTRACT

Objective: To study efficacy with fixed dose combination of latanoprost/ timolol versus brinzolamide/brimonidine in primary open angle glaucoma. **Material & Methods**: A prospective, randomized, comparative, clinical study was conducted on 50 patients. The patients were randomly divided in two groups of 25 each to receive following two treatments: Group A (n=25) Latanoprost and Timolol (0.005+0.5%w/v) ophthalmic solution once daily; Group B (n=25) Brinzolamide and Brimonidine (1%+0.15%w/v) ophthalmic solution thrice daily for 12 weeks. Efficacy assessment was done at the end of 2, 4, 6 and 12 weeks by observing Intra Ocular Pressure (IOP), visual acuity assessment, number of patients having headache, eye-ache & assessment of VAS score for headache & eyeache was also done. **Results**: Intraocular Pressure assessment using Goldmann applanation tonometer was done in both the groups. IOP in Group A at the end of 12 weeks was 19 as compared to 27.6 at the baseline while in group B it was 20 as compared to 26.76 at the baseline. The difference was statistically significant at the end of 12 weeks; $p<0.001$. Improvement in mean vision in Group A was more than Group B at the end of 12 weeks (33.3% Vs 15.2%) but the difference was not statistically significant. Reduction in VAS score for headache & eye-ache was more with Group A as compared to Group B at the end of 12 weeks but the difference was statistically different.

KEYWORDS: Latanoprost, Timolol, Brinzolamide, Brimonidine, Intra Ocular Pressure, Mean vision, headache, eye-ache, visual acuity score.

INTRODUCTION

Glaucoma is a term used to describe group of diseases of the eye characterized by progressive and irreversible damage to the optic nerve (chronic optic neuropathy) that are associated frequently with raised intraocular pressure (IOP) and with irreversible but preventable visual field loss, which if untreated can lead to blindness.[1,3] It is the second leading cause of blindness worldwide after cataracts.

Globally 57.5 million people were affected by POAG in 2015& the global prevalence was 2.2%.[2,70] Glaucoma is due to primary or secondary causes. Primary causes could be due to raised IOP or because of vascular insufficiency.[4] Rise in IOP in glaucoma can be due to increased rate of aqueous humor production or due to decrease in aqueous outflow facility.[5] Other risk factors include advancing age, family history, african ancestry, myopia and systemic diseases including diabetes & hypertension. IOP independent mechanisms of damage include reduced ocular perfusion pressure (association with vascular diseases such as diabetes, hypertension & migraine), excitotoxic damage from excessive glutamate, autoimmune-mediated nerve damage, loss of neurotropic factors, failure of cellular repair mechanisms and abnormal autoregulation of retinal & choroidal vasculature.[71] The disease is insidious and usually asymptomatic. Headache, eyeache of mild intensity, difficulty in reading and close work due to increasing accommodative failure as a result of constant pressure on the ciliary muscle and its nerve supply,, so patient complains of frequent change of presbyopic glasses, delayed dark adaptation, significant loss of vision and blindness.[10] In late stages, pupil reflex becomes sluggish and cornea may show slight haze & IOP is permanently raised above 21 mm of Hg.

Aim of the treatment is to lower IOP to a level where (further) visual loss does not occur. Basic principles of medical therapy of POAG include identification of target pressure by taking into account the severity of existing damage, the level of IOP, age and general health. From the baseline evaluation data a 'target pressure' (below which glaucomatous damage is not likely to progress)

should be identified for each patient. Progression is uncommon if IOP is maintained at less than 16 to 18 mm of Hg in patients having mild to moderate damage. Low target pressure (12-14mmHg) is required with severe damage.

Medications commonly used are prostaglandin analogues, topical beta blockers, adrenergic drugs and carbonic anhydrase inhibitors.[8] 40% patients need more than once medication to reach the target IOP as monotherapy is often insufficient to achieve target IOP and combination of two drugs i.e the one which decreases aqueous production (timolol or brimonidine or dorzolamide) and other drug which increases aqueous outflow (latanoprost or brimonidine or pilocarpine) is used. Fixed-combination therapies provide multiple benefits versus treatment with corresponding separate medications which include potentially lower cost, simplified treatment regimens, improved treatment compliance, reduced risk of drug wash out and decreased risk of corneal and ocular surface damage associated with cumulative exposure to preservatives.

Topical prostaglandin analogues decrease IOP by increasing the uveo-scleral outflow of aqueous.[15] They are considered as first line of treatment due to their once daily dosing, low incidence of systemic side effects and potent IOP lowering effect and have largely replaced beta adrenergic agonists as first line medical therapy for glaucoma. In a study done by Rouland et al, it was reported that mean IOP reduction at the end of 84 days after topical administration of preservative free latanoprost was 36% while benzalkonium chloride (BAK) preserved latanoprost it was 38%. As they have synergistic effect, they are combined to lower IOP in POAG. In a systemic review and meta- analysis done by Xing et al, a better IOP lowering effect has been demonstrated for fixed drug combination of latanoprost and timolol as compared to the components as monotherapy.[25] Combined treatment with brinzolamide and brimonidine is another effective option to lower IOP. Brinzolamide acts by inhibiting the enzyme carbonic anhydrase (CAI) in the ciliary epithelium resulting in decreased aqueous humour formation[10] while brimonidine, an alpha 2 adrenergic agonist decreases the formation of aqueous humour, leads to increase in uveoscleral outflow and it has neuroprotective action.[11] In study done by Katz et al and Aung et al it was concluded that fixed-combination of brinzolamide 1% and brimonidine 0.2% could safely and effectively lower IOP in patients with open-angle glaucoma and significantly superior IOP lowering activity was found compared with either brinzolamide or brimonidine monotherapy Thus, this study was conducted to assess and compare the effect of 2 Fixed dose combinations (FDCs) i.e latanoprost/timolol & brinzolamide/brimonidine in patients of primary open angle glaucoma.

To the best of our knowledge, no such study involving comparison of efficacy parameters with fixed dose combination of latanoprost/timolol versus brinzolamide/brimonidine in primary open angle glaucoma has been conducted worldwide. Hence, the present study was therefore taken.

METHODS

This was a prospective, open label, randomized, comparative clinical study conducted by the Department of Pharmacology and Ophthalmology, Pt. B. D. Sharma PGIMS, Rohtak on 50 patients. Study was in accordance with the principles of good clinical practice (ICH-GCP) and declaration of Helsinki. An informed consent was obtained from all patients enrolled for the study and the study was done after obtaining the ethical clearance from institutional ethical committee. No. IEC/18/pharma03 dated: 19.12.2018. Patients enrolled in the study were randomized with the help of computer generated random numbers to allocate the treatment schedule. Enrolment of patients was done as shown in fig.1.

Total 50 patients i.e. 25 in each group completed the study. The patients were randomly allocated to receive any of two different treatments. All the patients were explained about the study through patient information sheet and informed consent was obtained. The inclusion criteria included were- patient of either gender >18yrs of age, with baseline IOP more than 21 mm Hg in each eye requiring a fixed dose antiglaucoma drug combination and patient was eligible if best corrected visual acuity was at least 6/60 or better and visual field showed glaucomatous changes. Exclusion criteria included- patient with active ocular disease, hypersensitivity to study medications or other ocular medications that might have substantial effect on IOP, ocular surgeries in past 3 months, ocular inflammation and infection within past 3 months, ocular trauma within past 6 months, intraocular conventional surgery or laser surgery within past 6 months, glaucoma other than POAG, pregnant and lactating mother.

The eligible patients after screening were randomly allocated to one of the following treatments intraocularly for a period of 12 weeks: Group A received Latanoprost and Timolol (0.005+0.5% w/v) ophthalmic solution once daily and Group B received Brinzolamide and Brimonidine (1% +0.15% w/v) ophthalmic solution thrice daily. Available commercial preparations (same brand) of the drugs were used.

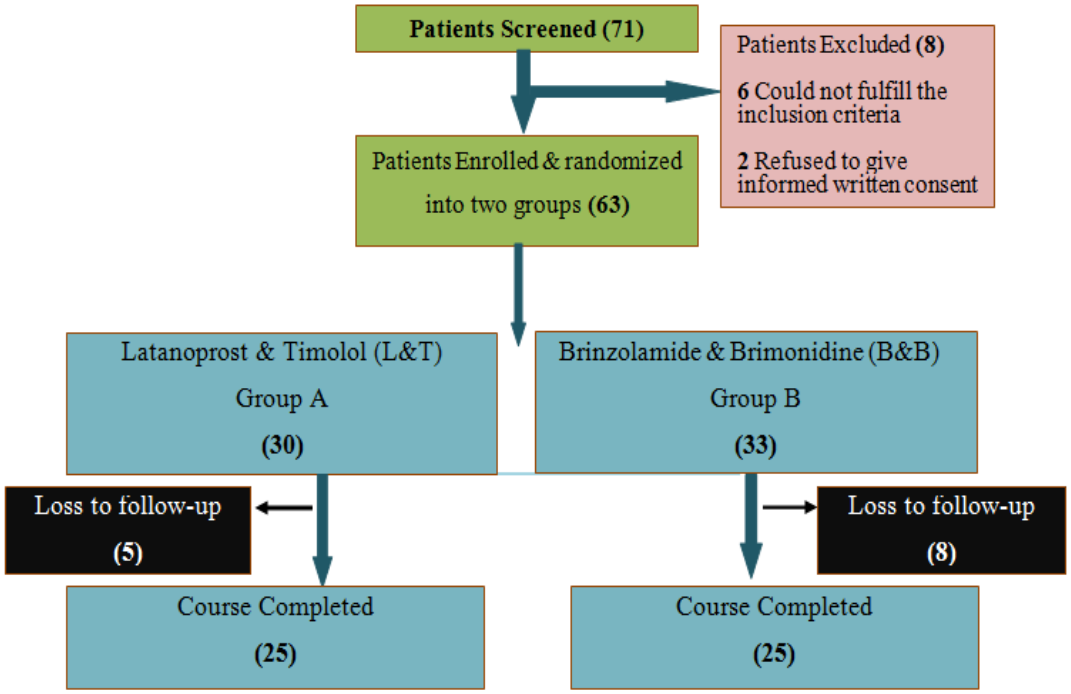

Fig 1: Enrolment of study population.

Headache, eyeache, improvement in mean vision, VAS score for headache & eyeache & Intraocular pressure assessment was done at baseline, 2, 4, 6 and 12 weeks. Intraocular Pressure assessment was done using Goldmann applanation tonometer.

Data was expressed as Mean ± SEM. Both intragroup and intergroup statistical analyses were done. Intragroup analysis for repeated measures was done using ANOVA while intergroup analysis was done using unpaired t test. A p-value <0.05 was considered as statistically significant & <0.001 was considered as statistically highly significant.

RESULTS

The patients in each group were found to be comparable at the time of their initial visit with regard to baseline characteristics such as age, weight, drug allergy and other parameters (Table 1).

Table 1: Comparison of study population characteristics.

Characteristics	GROUP A (L&T) (n=25)	GROUP B (B&B) (n=25)	'p' value
Age (years)	62.4±2.04	63.52±1.77	0.68
Weight (kg)	69.2±1.64	67.48±1.702	0.47
Gender			
Females	13	14	0.77
Males	12	11	
Education			0.08
Literate	17	22	
Illiterate	8	3	
History of drug allergy	--	--	--

Age and weight are expressed as Mean±SEM

- *Group A: Latanoprost and Timolol (L&T) (0.005+0.5% w/v FDC) ophthalmic solution once daily.*
- *Group B: Brinzolamide and Brimonidine (B&B) (1%+0.15% w/v FDC) ophthalmic solution thrice daily.*

In primary open angle glaucoma IOP is raised above 21 mm of Hg. Assessment of IOP was recorded in all the patients of either group before drug administration (baseline) and at end of 2,4,6 &12 weeks. Fig 1 shows the changes in IOP with the treatment. There was statistically highly significant reduction (*p<0.001*) in mean IOP with both the drugs i.e. latanoprost/timolol and brinzolamide/brimonidine at the end of 2 weeks which continued for 12 weeks. Mean IOP observed with latanoprost/timolol was 19 mmHg whereas with brinzolamide/brimonidine it was 20 mmHg at the end of 12 weeks as compared to baseline values. On inter-group analysis, mean IOP with latanoprost/timolol vs brinzolamide/brimonidine was 20.28 mmHg versus

21.68 mmHg at the end of 6 weeks (*p=0.01; statistically significant difference*) whereas it was 19 mmHg vs 20 mmHg (*p<0.001; statistically highly significant difference*) at the end of 12 weeks.

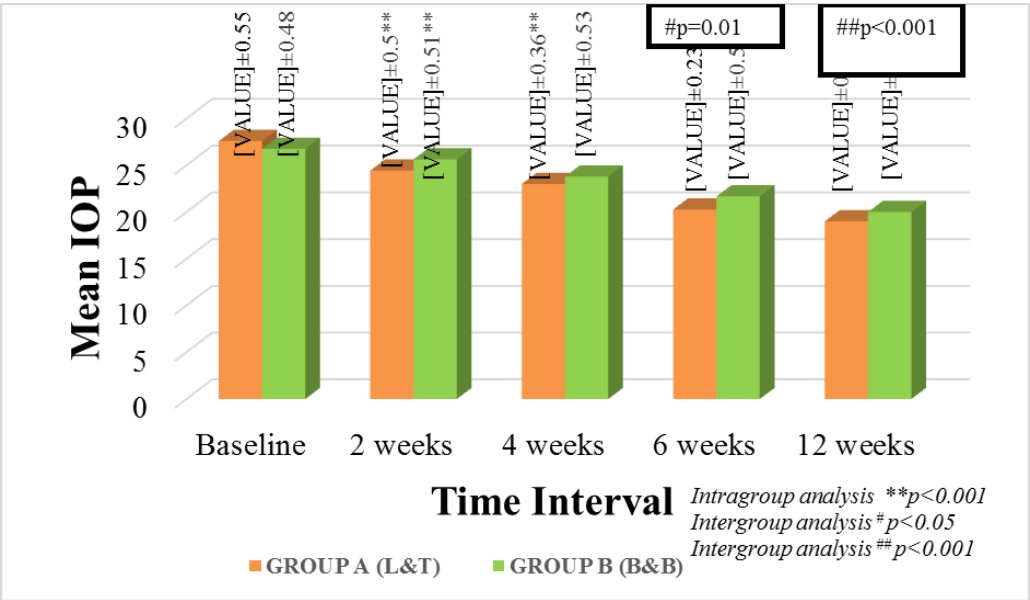

Fig. 1: Comparision of Mean IOP.

Mean vision was calculated in all the patients of either group before drug administration (baseline) and at the end of 2,4, 6 & 12 weeks. Snellen's fractions is converted to decimal form. Then using the formula [LogMAR = -log (snellen decimal)] all those decimals are converted into logMAR scale]. In L&T and B&B group at the end of 6 weeks reduction in LogMar (improvement in mean vision) which is statistically highly significant compared to baseline (p<0.001). In both the groups, this statistically highly significant improvement was maintained till the end of 12 weeks. Better results but not significant results were seen in L&T group as there was reduction in LogMar (improvement in mean vision) 33.33% while reduction in LogMar (improvement in mean vision) was 15.2% in B&B at the end of 12 weeks.

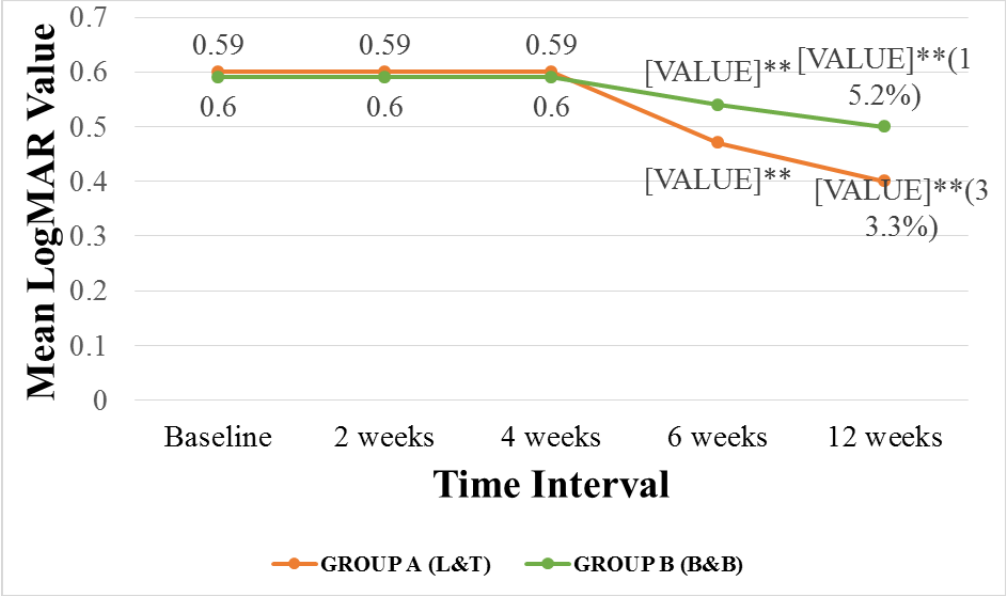

Fig. 2: Comparison of mean vision.

INTRAGROUP ANALYSIS

*** Comparison of values at end of week 6 and 12 with baseline values is showing statistically highly significant difference (p<0.001).*

Patient's condition for chronic headache was assessed on VAS scale which is a 10 cm horizontal scale. The left border represented "very good" condition and the severity of disease increased to right, accordingly the right border was characterized as "very poor" condition.

VAS score was calculated in all the patients of either group before drug administration (baseline) and at the end of 2, 4, 6 &12 weeks. Number of patients with headache were calculated in all the patients of either group before drug administration (baseline) and at the end of 2, 4, 6 &12 weeks. Analysis of VAS scale in the present study showed that there was highly statistically significant difference observed on comparison with baseline in both the groups at the end of 4, 6 and 12 weeks (p-value <0.001). On comparing both the groups, there was more reduction in VAS score in L&T group as compared to B&B group but it was statistically significant at the end of 6 weeks (p-value =0.03). Number of patients having headache were 4% at the end of 12 weeks versus 92% at baseline in L&T group whereas they were 16% in B&B group at the end of 12 weeks versus 100% at baseline but on comparing both the groups no statistically significant difference was observed at the end of the study.

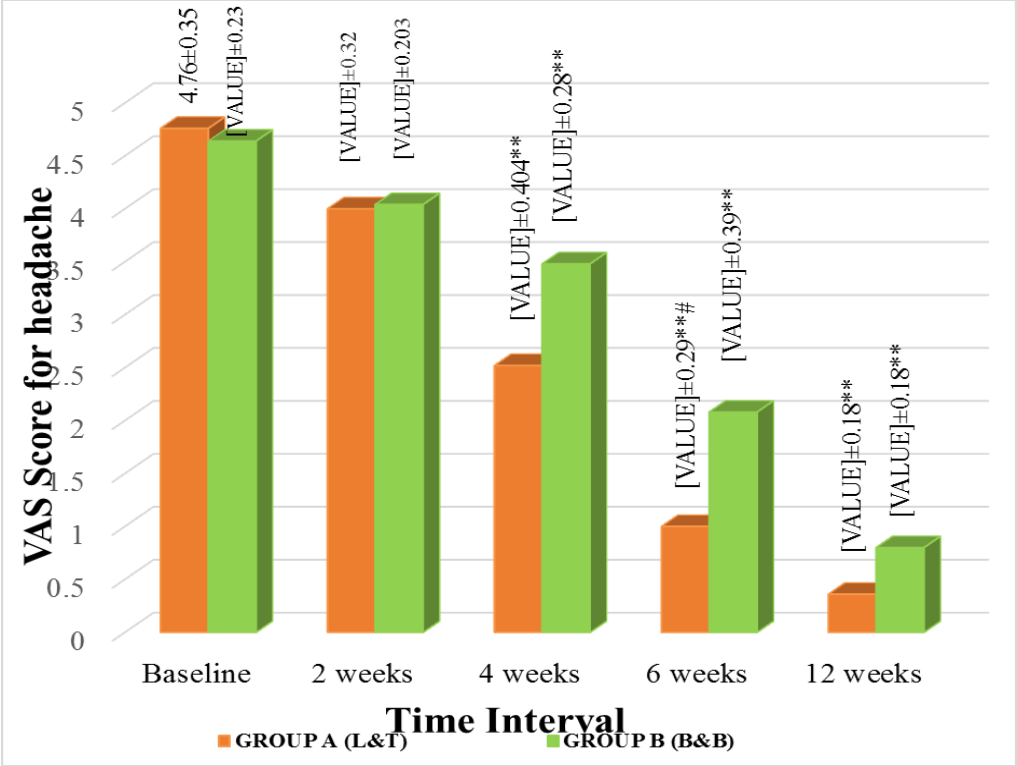

Fig. 3: Comparison of changes in VAS Score for headache.

- All values are expressed as Mean±SEM.
- Group A: Latanoprost and Timolol (L&T) (0.005+0.5% w/v FDC) ophthalmic solution once daily.
- Group B: Brinzolamide and Brimonidine (B&B) (1%+0.15% w/v FDC) ophthalmic solution thrice daily.

INTRAGROUP ANALYSIS

** *Comparison of values at end of week 12 with baseline values showing statistically highly significant difference. (p<0.001)*

INTERGROUP ANALYSIS

Comparison of values between Group A and B showing statistically highly significant difference at 12 weeks. (p<0.05)

Table 2: Distribution of Patients With Headache.

Headache	Group A (L&T) (n=25)	Group B (B&B) (n=25)	'p' value (Intergroup)
	No. of patients (%)	No. of patients (%)	
Baseline	23(92%)	25 (100%)	0.14
2 weeks	23 (92%)	25 (100%)	0.14
4 weeks	18 (72%)*	18 (72%)*	--
6 weeks	10 (40%)**	12 (48%)**	0.55
12 weeks	1 (4%)**	4 (16%)**	0.15

- All values are expressed as number of patients (percentage)
- Group A: Latanoprost and Timolol (L&T) (0.005+0.5% w/v FDC) ophthalmic solution once daily
- Group B: Brinzolamide and Brimonidine (B&B) (1%+0.15% w/v FDC) ophthalmic solution thrice daily

INTRAGROUP ANALYSIS

**Comparison of values at end of week 4 with baseline values is showing statistically significant difference (p<0.05).*

*** Comparison of values at end of week 6 and 12 with baseline values is showing statistically highly significant difference (p<0.001).*

INTERGROUP ANALYSIS

Comparison of values between Group A and B is not showing statistically significant difference (p>0.05)

Patient's condition for chronic eyeache was assessed on VAS scale which is a 10 cm horizontal scale. The left border represented "very good" condition and the severity of disease increased to right, accordingly the right border was characterized as "very poor" condition. VAS score was calculated in all the patients of either group before drug administration (baseline) and at the end of 2,4, 6 &12 weeks. Number of patients with eyeache were calculated in all the patients of either group before drug administration (baseline) and at the end of 2, 4, 6 &12 weeks. Analysis of VAS scale in the present study showed that there was statistically highly significant reduction in VAS score at the end of 4,6 and 12 weeks compared to baseline values in both the groups. (p-value <0.001). On comparing both the groups, there was more reduction in VAS score in L&T group as compared to B&B group but it was not statistically significant. Number of patients having eyeache were 20% at the end of 12 weeks versus 100% at baseline in both the groups.

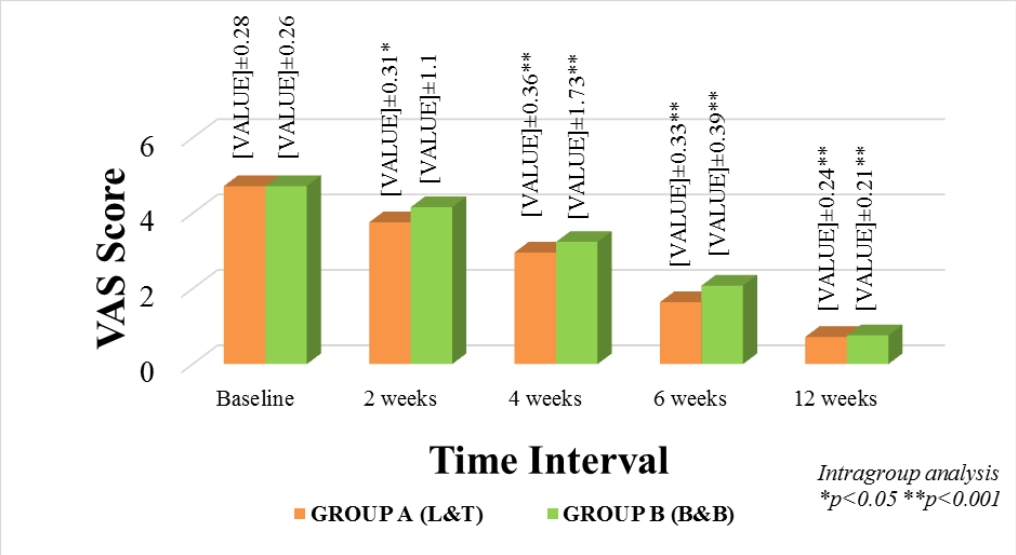

Figure 4: Comparison of changes in VAS Score for eyeache.

INTRAGROUP ANALYSIS

**Comparison of values at end of week 4 with baseline values is showing statistically significant difference (p<0.05).*

*** Comparison of values at end of week 6 and 12 with baseline values is showing statistically highly significant difference (p<0.001).*

Table 5: Distribution of Patients With Eyeache.

Eyeache	Group A (L&T) (n=25)	Group B (B&B) (n=25)	'p' value (Intergroup)
	No. of patients (%)	No. of patients (%)	p value
Baseline	25 (100%)	25 (100%)	--
2 weeks	24 (96%)	25 (100%)	0.32
4 weeks	21 (84%)	22 (88%)	0.68
6 weeks	15 (60%)**	18(72%)*	0.37
12 weeks	5 (20%)**	5 (20%)**	--

- All values are expressed as number of patients (percentage)
- Group A: Latanoprost and Timolol (L&T) (0.005+0.5% w/v FDC) ophthalmic solution once daily
- Group B: Brinzolamide and Brimonidine (B&B) (1%+0.15% w/v FDC) ophthalmic solution thrice daily

INTRAGROUP ANALYSIS

**Comparison of values at end of week 6 with baseline values is showing statistically significant difference (p<0.05) in group B.*

***Comparison of values at end of week 12 with baseline values is showing statistically highly significant difference (p<0.001) in group A and B .*

*** Comparison of values at end of week 6 with baseline values is showing statistically highly significant difference (p<0.001) in group A.*

INTERGROUP ANALYSIS

Comparison of values between Group A and B is not showing statistically significant difference. (p>0.05)

DISCUSSION

Glaucoma is a term used to describe group of diseases of the eye characterized by progressive and irreversible damage to the optic nerve & associated frequently with raised intraocular pressure (IOP)[3] and which if untreated can lead to blindness.[1] More than 60 million cases of glaucoma are there worldwide and it is estimated to increase to 80 million by 2020.[2] It is the second leading cause of blindness in world accounting for upto 8% of total blindness.

Rise in IOP in glaucoma can be due to increased rate of aqueous humor production or due to decrease in aqueous outflow facility. The disease is insidious and usually asymptomatic. Headache, eyeache of mild intensity and significant loss of vision and blindness.[10] A variation in IOP of over 5mmHg (Schiotz tonometer) is suspicious and over 8mm Hg is diagnostic of glaucoma.[10]

Exact similar studies were not available in which similar treatment groups were assessed for, mean IOP, vision, VAS scale for chronic headache & eyeache, number of patients of headache & eyeache.

Analysis of mean IOP score in the present study showed that there was highly statistically significant difference observed on comparison with baseline in both the groups at the end of 2,4, 6 and 12 weeks (p-value <0.001). On comparing both the groups, there was more reduction in IOP in L&T group as compared to B&B group but it was statistically significant at the end of 6 weeks & 12 weeks (p-value<0.05 & p-value <0.001) respectively. In a systemic review and meta- analysis done by Xing et al, a better IOP lowering effect & lower IOP fluctuation has been demonstrated for fixed drug combination of latanoprost and timolol (FCLT) as compared to the components as monotherapy. The findings of our study are similar to above mentioned study in the context that Latanoprost/Timolol FDC led to statistically significant reduction in mean IOP in our study as well as in the above mentioned systematic review. But exact comparison is not possible because in above mentioned systematic review they have compared Latanoprost/Timolol FDC with monotherapy of these drugs & with unfixed combination but we have compared Latanoprost/Timolol FDC with another FDC of Brinzolamide/Brimonidine.

In another study done by Schwenn et al, subjects were given Latanoprost/Timolol FDC once daily. Mean change in IOP from baseline of -4.0 ± 4.31 mmHg was noted at 6 months and this decrease was maintained and reductions were statistically significant throughout the follow-up.[26] The findings of our study are similar to above mentioned study in the context that Latanoprost/Timolol FDC led to statistically significant reduction in mean IOP in both the studies. However, exact comparison is not possible because in our study final reading of mean IOP was noted at end of 3 months whereas it was taken at end of 6 months & 24 months in the above mentioned study.

In a study done by Yilmaz et al, which included 54 patients with POAG who had failed to reach an IOP of ≤21 mmHg while receiving bilateral monotherapy of hypotensive lipids for least 28 days. In this study effect of fixed combination of bimatoprost/timolol maleate (BTFC), latanoprost/timolol maleate (LTFC), and travoprost/timolol maleate (TTFC) was observed on 24hr IOP. The findings of our study are similar to above mentioned study in the context that L &T FDC led to reduction in IOP for 24 hrs in our study as well as in above mentioned study. However, intergroup comparison is not possible. L &T FDC was compared with TTFC & BTFC in above mentioned study whereas it was compared with B&B FDC in our study.

In studies done by Özyol et al, Latanoprost/timolol fixed dose combination (Lat/T-FDC) versus Latanoprost/timolol unfixed combination (Lat/T-UFDC) gel-forming solution in glaucomatous patients, in 8-weeks study on 90 patients, mean IOP reduction from baseline to each visit (4 & 8 weeks) was significant in both groups (p<0.01). It was concluded that the concomitant solution Lat/T-UFDC gel led to a larger significant additional IOP reduction and lower daytime IOP levels as compared with the fixed combination.[82]

The findings of our study are similar to above mentioned study in the context that the drugs Latanoprost &Timolol in FDC were used in the same concentration (0.005%+0.5%w/v) as in above mentioned study & statistically highly significant improvement was seen in both the studies. However better IOP reduction was observed in our study with L&T FDC than above mentioned study i.e. 7.32 mm Hg at 6 weeks in our study & 3.2±2.1 mm Hg at 8 weeks in above mentioned study. The reason could be sample size was smaller in our study as compared to above mentioned study.

Mean vision was calculated in all the patients of either group before drug administration (baseline) and at the end of 2,4, 6 & 12 weeks. Snellen's fractions is converted to decimal form. Then using the formula [LogMAR = -log (snellen decimal)] all those decimals

are converted into logMAR scale]. In both the groups, this statistically highly significant improvement was maintained till the end of 12 weeks. Better but not significant results were seen in L&T group as there was reduction in LogMar (improvement in mean vision) 33.33% while reduction in LogMar (improvement in mean vision) was 15.2% in B&B at the end of 12 weeks.

Analysis of VAS scale of headache in the present study showed that there was highly statistically significant difference observed on comparison with baseline in both the groups at the end of 4, 6 and 12 weeks (p-value <0.001). In L&T group and B&B group mean decrease in VAS score was 47.05% and 25% respectively at the end of 4 weeks compared to their baseline values (p-value <0.001) which was maintained till end of 12 weeks in both the groups. On comparing both the groups, there was more reduction in VAS score in L&T group as compared to B&B group but it was statistically significant at the end of 6 weeks (p-value =0.03). On comparing number of patients having headache no statistically significant difference was observed at the end of the study.

Analysis of VAS scale of eyeache in the present study showed that there was statistically highly significant reduction in VAS score at the end of 4,6 and 12 weeks compared to baseline values in both the groups (p-value <0.001). On comparing both the groups, there was more reduction in VAS score in L&T group as compared to B&B group but it was not statistically significant.

CONCLUSION

1. Both the treatment groups i.e Latanoprost/Timolol and Brinzolamide/Brimonidine. were found to be efficacious in patients having primary open angle glaucoma (led to intraocular pressure reduction, improvement in headache, eye ache and visual acuity)
2. Latanoprost/Timolol was significantly more effective than Brinzolamide/Brimonidine as reduction in IOP was more and progression of disease was less.
3. Latanoprost/Timolol showed early response in improvement of headache.