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A COMPARATIVE STUDY OF TWO FIXED DOSE COMBINATIONS IN PRIMARY OPENANGLE GLAUCOMA

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ABSTRACT

Objective: To study efficacy & safety of fixed dose combination of latanoprost/timolol versus brinzolamide/brimonidine in primary open angle glaucoma. **Methods**: A prospective, randomized, comparative, clinical study was conducted on 50 patients. The patientswere 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 atthe end of 2, 4, 6 and 12 weeks by observing Intra Ocular Pressure (IOP) changes from baseline. At baseline & 12 weeks number of patients having IOP less than or equal to 18 mm Hg, visual field defect with automated perimetry & optic disc changes by dilated fundoscopy were seen. Overall improvement was observed from baseline with the clinical global impression improvement scale (CGI-I). Safety assessment of both the groups was also done. **Results**: At the end of 2,4,6 and 12 weeks, statistically highly significant reduction in mean IOP from baselinewas observed in both the groups but reduction was more in group A as compared to group B (31.1% Vs 25.2%; $p<0.001$) at the end of 12 weeks. Number of patients having IOP less than or equal to 18 mm of Hg was also more in group A Vs group B (25% Vs 4%; $p<0.05$) at the end of 12 weeks. Visual field defect, optic- cup to disc ratio showing progression of disease was more in group B. CGI-I scale was statistically highly significantwith group A better than Group B (70.37% Vs 45.25%). Safety profile was better in group A than group B. **Conclusion**: Latanoprost/Timolol was found to be more efficacious & safer than Brinzolamide/ Brimonidinecombination in primary open angle glaucoma

KEYWORDS: Latanoprost, Timolol, Brinzolamide, Brimonidine, Intra Ocular Pressure, Visual field defect,optic-cup to disc ratio, Clinical global impression improvement.

INTRODUCTION

Glaucoma is a term used to describe group of diseases of the eye characterized by progressive and irreversible damage to the optic nerve and which if untreated can lead to blindness.[1] Globally 57.5 million people were affected by POAG in 2015, rising to 65.5 million by 2020.[2]

POAG affects 1 in100 in general population (of either sex) above the age 40 years.[3] 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 todecrease in aqueous outflow facility.[5] It is asymptomatic but defect in visual field & significant loss of vision, scotoma (defect in visual field) and blindness can occur. In late stages, pupil reflex becomes sluggishand cornea may show slight haze & IOP is permanently raised above 21 mm of Hg.[6] The visual field loss gradually spreads centrally as well as peripherally, and eventually only a small island of central vision (tubular visual field) and accompanying temporal island are left.[7]

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. Ocular

medications have adverse effect including ocular irritation, blurring of vision and burning of eyes.

Prostaglandin(latanoprost) decreases the IOP by increasing the uveoscleral outflow of aqueous and is considered drug of choice in POAG provided the patient can afford to buy it.[9] Topical beta blocker (timolol) lowers IOP by reducing aqueous secretion and is recommended as the drug of choice for medical therapy of POAG in poor or having average socioeconomic status.[9] As they have synergistic effect, they are combined to lower IOP in POAG. 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]

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.

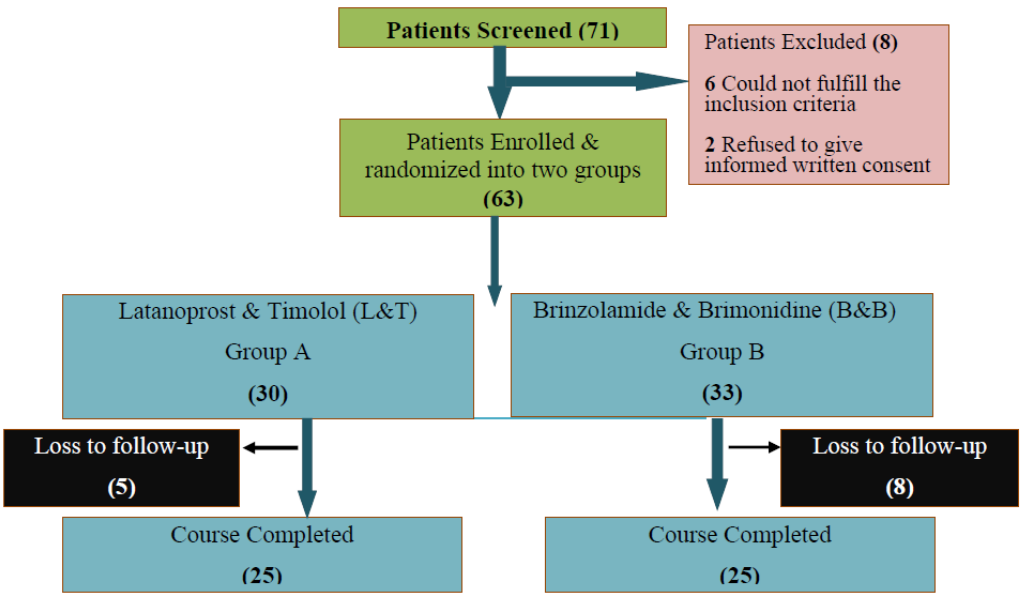


Fig 1: Enrolment of study population.

Intraocular pressure assessment and safety assessment were done at baseline, 2, 4, 6 and 12 weeks.

Intraocular Pressure assessment was done using Goldmann applanation tonometer. At baseline & 12 weeksassessment of number of patients less than 18 mm Hg, visual field testing, dilated fundoscopy and clinical global impression-improvement scale (CGI-I) to observe overall improvement were done. Visual field testing was done by automated perimetry **t**o detect glaucomatous changes in visual field. Dilated fundoscopywas done with 1% tropicamide and 2.5% phenylephrine to detect optic-cup disc ratio. Optic- cup disc ratio more than 0.5 was labelled as suspicious for glaucoma & subsequently it was repeated to observe any progression of disease. Increase in this ratio denotes progression of disease. Clinical global impression- improvement scale (CGI-I) was done at the end of study (12 weeks), to assess patient's overall clinical condition. Compared to the patient's condition at start of medication, this patient's condition was analyzed as the scoring system i.e. 1=very much improved; 2=much improved; 3=minimally improved; 4=no change from baseline; 5=minimally worse; 6=much worse;7=very much worse since the initiation of treatment.

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			0.77
Females	13	14	
Males	12	11	
Education			0.08
Literate	17	22	
Illiterate	8	3	
History of drugallergy	--	--	--

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 &12weeks. Table 2 shows the changes in mean IOP reduction 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. Reduction observed with latanoprost/timolol was 31.1% whereas with brinzolamide/brimonidine it was 25.2% at the end of 12 weeks as compared to baseline values. On inter-group analysis, reduction of mean IOP with latanoprost/timolol vs brinzolamide/brimonidine was 26.5% versus 18.9% at the end of 6 weeks (*p=0.01; statistically significant difference*) whereas it was 31.1% vs 25.2% (*p<0.001; statistically highly significant difference*) at the end of 12 weeks. There was reduction in number of patients having IOP less than or equal to 18 mm Hg with both the groups at the end of 12 weeks. Reduction observed with latanoprost/timolol was 20% whereas with brinzolamide/brimonidine it was 4% as compared to baseline values but the reduction was not statistically significant. However, on comparing both the groups the difference was statistically significant at the end of 12 weeks *(p=0.01).* At the end of 12 weeks there was deterioration in the visual field defect on automated perimetry with brinzolamide/brimonidine FDC only as 36% patients had visual field defect outside normal limit compared to 28% at baseline, however the deterioration was not statistically significant. However, the visual field defect remailed same with latanoprost/timolol combination i.e. 28% at baseline & at 12 weeks had visual field defect outside normal limits. Optic cup to disc ratio seen on dilated fundoscopy only increased (3.03%) in brinzolamide/brimonidine group whereas remained same in latanoprost/timolol group, thus progression of disease was observed only in brinzolamide/brimonidine group but it was not statistically significant. Clinical global impression-improvement scale (CGI-I) score showed statistically highly reduction (*p<0.001)* in both the groups. Reduction observed with latanoprost/timolol was 70.37% whereas with brinzolamide/brimonidine it was 45.25% as

compared to baseline values & on comparing both the groups the difference was statistically highly significant at theend of 12 weeks ($p<0.001$) as shown in fig 2.

Table 2: Comparison of mean IOP.

Mean IOP (mm Hg)	GROUP A(L&T) (n=25)		GROUP B(B&B) (n=25)		'p' value (Intergroup)
	Mean± SEM	Reduction (%)	Mean± SEM	Reduction (%)	p value
Baseline	27.6±0.55		26.76±0.48		0.25
2 weeks	24.44±0.5	3.16** (11.4%)	25.64±0.51	1.12** (4.1%)	0.105
4 weeks	23±0.36	4.6** (16.6%)	23.8±0.53	2.96** (11.1%)	0.22
6 weeks	20.28±0.23	7.32** (26.5%)	21.68±0.51	5.08** (18.9%)	0.01#
12 weeks	19±0.1	8.6** (31.1%)	20±0.17	6.76** (25.2%)	<0.001#

- 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 2,4, 6 and 12 with baseline values showing statistically significant difference ($p<0.05$).*

** *Comparison of values at end of week 2,4, 6 and 12 with baseline values showing statistically highly significant difference ($p<0.001$).*

INTERGROUP ANALYSIS

Comparison of values between Group A and B showing statistically significant difference at 6 weeks. ($p<0.05$)

Comparison of values between Group A and B showing statistically highly significant difference at 12 weeks. ($p<0.001$)

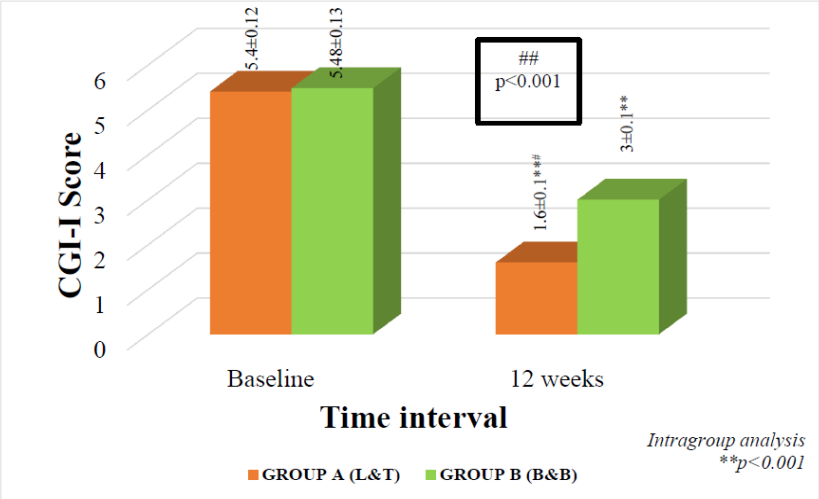


Fig 2: Comparison of CGI-I Score.

- 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. ($p<0.001$)*

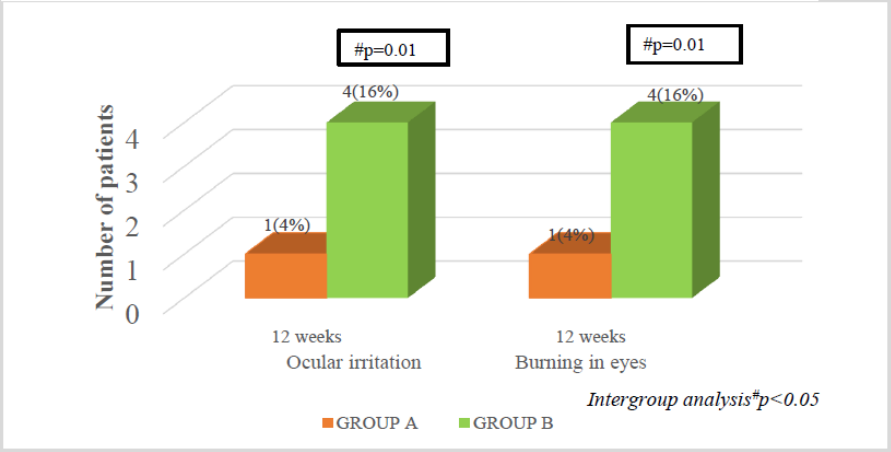
INTERGROUP ANALYSIS

Comparison of values between Group A and B showing statistically highly significant difference at 12 weeks. ($p<0.001$)

The patients were observed for the side effects like conjuctival hyperaemia, ocular irritation, ocular pain, blurring of vision, iris pigmentation, eyelash growth, burning in eyes, eye allergy, conjunctivitis, conjuctival follicles, dysgeusia, dry mouth & fatigue. Both the groups were found to be quite safe as only two adverse drug reactions were noted with both the groups i.e. ocular irritation and burning in eye. At the end of 2,4,6 and 12 weeks number of patients having ocular irritation and burning in eyes in latanoprost/timolol were 1(4%), 1(4%), 1(4%) and 1(4%) respectively whereas in brinzolamide/brimonidine were 2 (8%), 3

(12%), 3 (12%), and 4 (16%) patients respectively.

Latanoprost/timolol showed better response than brinzolamide/brimonidine as number of patients having ocular irritation and burning in eyes at the end of 12 weeks were less as compared to latter & the difference was statistically significant (4 versus 16% ;p-value=0.01) regarding both types of adverse drug reactions. No systemic adverse drug reaction was reported by any of the patient of either group as shown in fig 3.



- All values are expressed as number of patients
- 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.

INTERGROUP ANALYSIS

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

DISCUSSION

Glaucoma (or Glaucosis) is an ophthalmological disease & recognized as a disease entity in the 17th century.[1] There is progressive optic neuropathy resulting in specific pattern of irreversible visual field defects. Rise in IOP in POAG occurs due to decrease in aqueous outflow facility (drainage of aqueous humor is through trabecular meshwork 70-80% and uveoscleral outflow 20-30%).[5] On fundus examination, glaucomatous changes in the optic disc can be described as early, advanced and glaucomatous optic atrophy.[6] The visual field loss gradually spreads centrally as well as peripherally. Significant loss of vision and blindness occurs in glaucoma.

Exact similar studies were not available in which similar treatment groups were assessed for reductionin mean IOP from baseline, number of patients having IOP <18mmHg, visual field defects, optic-cup disc ratio, clinical global improvement and safety profile.

In a meta-analysis done by Lou et al, all the combinations i.e. bimatoprost/timolol (BTFC), latanoprost/timolol (LTFC) and travoprost/timolol (TTFC) led to statistically significant reduction in IOP done on 991 patients. LTFC was as effective as TTFC. All the results were statistically significant.[12] Our study is similar in the context that L&T FDC led to reduction in IOP in our study as well as in above mentioned study and the results were statistically significant.

In a study done by Kothy et al, on 52 glaucoma patients out of which 39 were primary open angle glaucoma treated with brinzolamide 1% and brimonidine 0.2% (BBFC). All patients used BBFC twice daily at intervals of approximately 12 h. The IOP on the study eyes was 21.2 ± 3.7 mmHg before and 16.9 ± 2.6, 16.0 ± 2.2, 17.6 ± 3.1 and 18.0 ± 3.1 mmHg after the introduction of BBFC at month 1, 3, 6 and 12, respectively ($p < 0.0003$ for all time points compared to baseline).[13] The findings of our study are similar to above mentioned study in the context that BBFC led to statistically highly significant reduction in IOP in both the studies. The findings of our study are different to above mentioned study in the context that better response was seen at 1 month in above mentioned as compared to our study (4.3 reduction Vs 2.96 reduction of IOP respectively) in ours study but better response was seen at 3 months in our study (6.76 reduction Vs 5.2 reduction of IOP respectively). The reason could be sample size was smaller in our study as compared to above mentioned study. Moreover, B&B FDC was given intra-ocularly thrice daily as brinzolamide 1% plus brimonidine 0.15% in our study unlike above mentioned study in which it was given twice daily as brinzolamide 1% plus brimonidine 0.2%.

In a study done by Gandolfi et al, a randomized trial of brinzolamide and brimonidine as concomitant therapy versus brinzolamide 1% plus brimonidine 0.2% as FDC for open angle glaucoma or ocular hypertension in a 6-month trial in which follow up visits were 2 weeks, 6 weeks, 3 months & 6 months. The percentage of patients

with IOP less than 18 mmHg across study visits was 68.9–71.6% for those receiving BBFC and 65.8–71.6% for those receiving brinzolamide and brimonidine as concomitant therapy. Thus percentage of patients achieving IOP less than18 mmHg was similar with both treatments at the time of peak morning.[14] Number of patients with IOP less than 18 mmHg also increased at the end of our study like the above study. The findings of our study are different to above mentioned study in the context that our study was of 3 months unlike the above study which was of 6 months duration and the increase in percentage of patients having IOP less than 18 mmHg was comparatively less than in above mentioned study.

In a crossover study done by García-López et al, on 78 patients in which once-daily bimatoprost 0.03%/timolol 0.5% or twice-daily dorzolamide 2% brimonidine 0.2% /timolol0.5% was given. Patients received the opposite medication for 3 months before returning to their pre-baseline medication for 3 months. During the first treatment period, a significant percentage of patients achieved an IOP response <14 mm Hg in both treatment groups, compared with baseline, but the percentage was almost twice as high in the bim/tim group. In addition, the level of IOP lowering was maintained in patients switched from dorz/brim/tim to bim/tim during the second treatment period. 70% of patients on bim/tim at month 3 had anIOP <14 mm Hg, which declined to 58% at month 6 (i.e, after 3 months of dorz/brim/tim treatment). In patients receiving dorz/brim/tim at month 3, 38% had an IOP <14 mm Hg, which remained comparable afterreturn to bim/tim.[15] The findings of our study are similar to above mentioned study in the context that ours study was prospective study & number of patients with IOP less than 18 mmHg also increased at the end of 3 months like the above study. Additionally, here also prostaglandin/timolol fixed dose combination has shown much better & sustained response than carbonic anhydrase & alpha 2 agonist fixed combination. The findings of our study are different to above mentioned study in the context that our study was of 3 months unlike the above study which was of 6 months duration. Additionally, above study was cross-over unlike our study & number of patients enrolled were more than our study.

In a systemic review and meta- analysis done by Xing et al, fixed drug combination of latanoprost and timolol as compared to the components as monotherapy was studied for the period of 10 weeks. However no statistically significant difference for the incidence of visual field defect was observed.[16]

In a study done by Schwenn et al, on Lat/T-FDC once daily on 2339 patients. Changes from baseline in horizontal and vertical cup/disc ratios showed a tendency toward stability and were not considered to be clinically significant.[17] The findings of our study are similar to above mentioned study in the context that nodifference in optic-cup disc ratio was seen, thus there is no disease progression in L&T group. The findingsof our study are different to above mentioned study in the context that optic -disc ratio was studied for 3 months duration whereas in the above mentioned it was studied for 24 months and both horizontal and vertical optic-disc ratios were seen unlike our study in which only vertical cup disc ratio was seen.

In critical appraisal done by Nguyen et al in which quality of life of different FDCs was compared, it was observed that the incidence of eye burning/stinging/irritation was upto 5.4% with BBFC compared with timolol (up to 18.1%) at 3 months. However, it was greater with BBFC (6.3%) than timolol (4.5%) at 6 months.[18] The results of our study are similar to the critical appraisal done in above mentioned study at 3 months in view of the fact that BBFC led to burning as well as irritation in both of the studies. However, the incidence was more in our study (16%) whereas it was only 5.4% at the end of 3 months in above mentioned study. Moreover, in our study we have compared LTFC with BBFC whereas in the above study they have compared timolol with BBFC.

In a study done by Moosavi et al, done on 76 patients where fixed dose combination (BBFC 1% brinzolamide/0.2%brimonidine) was given. BBFC intolerance was in 13% patients.[86] The results of above study is similar to our study in the context that in our study ocular irritation due to BBFC was in 16% patientswhereas in the above study BBFC intolerance was in 13% patients.[19]

In a study done by Higginbotham et al, latanoprost and timolol FDC was compared with monotherapy of these drugs. Of the 418 randomized patients, 258 reported adverse events that occurred in 1% or more of the patients. The most common complaint was irritation of the eye (in 46 of the 418 subjects). Investigators noted hyperemia involving the bulbar conjunctiva in 9 patients in the fixed combination therapy group and in 18 in the latanoprost group. Four patients reported hypertrichosis (2 each in the fixed combination therapy and latanoprost groups). Two latanoprost-treated patients and 2 patients receiving fixed combination therapy reported increased iris pigmentation.[88] The results of our study are similar to the above mentioned study in view of fact that ocular irritation was observed in both the studies whereas incidence was 4% with L&T in our study as compared to about 11% in above mentioned study. However, no hyperemia, hypertrichosis and iris pigmentation was observed in our study whereas it was seen with L&T FDC in above mentioned study.[20]

CONCLUSION

Both the treatment groups i.e Latanoprost/Timolol and Brinzolamide/Brimonidine were found to be safe and efficacious in patients having primary open angle glaucoma (led to intraocular pressure reduction)

1. Latanoprost/Timolol was significantly more

effective than Brinzolamide/Brimonidine as reduction in IOP was more and progression of disease was less.

2. Brinzolamide/Brimonidine led to more adverse drug reactions than Latanoprost/Timolol i.e. ocular irritation and burning in eyes.

However, more studies observing the effect of treatment on efficacy parameters would be beneficial in order to provide guidance in making clinical decision to prescribing physicians.

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CONFLICTS OF INTEREST: There Are No Conflicts Of Interest.

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