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RESEARCH ARTICLE

Evaluation of efficacy of the fixed *vs* unfixed combination of latanoprost and timolol in patients of open-angle glaucoma and ocular hypertension insufficiently controlled on timolol and latanoprost monotherapy

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ABSTRACT

Background: Glaucoma is a term describing a group of ocular disorders with multifactorial etiology united by a clinically characteristic intraocular pressure (IOP) associated optic neuropathy. Elevated IOP is identified as the only known risk factor which can be modified by anti-glaucomatous treatments. Patients who do not achieve target IOP levels with a single ocular hypotensive agent often are prescribed concomitant therapy with a medication that has a different mechanism of action. **Aims and Objectives:** The aim was to evaluate the efficacy of the fixed and unfixed combinations of latanoprost and timolol in patients of open-angle glaucoma and ocular hypertension (OH). **Materials and Methods:** A comparative randomized open-label trial was conducted on newly diagnosed patients of open-angle glaucoma and OH who were receiving either latanoprost 0.005% once daily or either timolol SR 0.5% once or twice daily in the preceding 4 weeks and whose IOP was not controlled with the prior monotherapy of latanoprost or timolol and remained ≥21 mmHg were included in the study. Patients were randomized to two groups to receive the following medication - Group I: Fixed combination eye drops of latanoprost (0.005%) and timolol SR (0.5%), once a day, in the dose of 1 drop at 9 LTFC and Group II: Unfixed combination of latanoprost (0.005%), once a day in the dose of 1 drop at 9 pm and timolol SR (0.5%), once a day in the dose of 1 drop at 9 am (LTuFC). Patients were evaluated at 0, 2, 4, 6, and 12 weeks for the assessment of IOP and Visual acuity. **Results:** Both LTFC (Group I) and LTuFC (Group II) caused a reduction in IOP which was statistically highly significant ($P < 0.01$) at all the intervals but on comparison both the groups affected the IOP in a similar fashion and demonstrated no difference statistically ($P > 0.05$). **Conclusion:** Both the regimens on comparison revealed similar efficacy thereby failing to prove superiority over each other. Thus, the clinicians have a wider choice of fixed or unfixed combinations of latanoprost and timolol, when monotherapy of either drug fails.

KEY WORDS: Timolol SR; Latanoprost; Eye Drops; Open Angle Glaucoma; Ocular Hypertension; Fixed Combination Eye Drops

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INTRODUCTION

Glaucoma is a term describing a group of ocular disorders with multifactorial etiology united by a clinically characteristic intraocular pressure (IOP) associated optic neuropathy,[1] a definite causal relationship has been reported between the level of IOP and damage to the optic nerve with resultant

change in visual field[2] Raised IOP is seen in a vast number of ocular conditions, but the two most common ocular diseases associated with increased IOP are glaucoma and ocular hypertension (OH).[3] It was estimated that worldwide about 66.8 million people had visual impairment from glaucoma, with 12.5 million suffering from blindness.[4] About 12.8 million patients suffer from glaucoma in India[5] of the various types of glaucomas, primary open-angle glaucoma (POAG) is the most common form of glaucoma throughout world, accounting for about two-third of cases.[6]

Elevated IOP is identified as the only known risk factor which can be modified by anti-glaucomatous treatments.[7] Among the various ocular hypotensive drugs, beta-blockers like timolol,carteolol, etc. and prostaglandin analogs such as latanoprost, travoprost are playing an increasingly important role in the first-line therapy of glaucoma[6,8] The ocular hypotensive effect of once daily 0.5% timolol ranges from 17% to 28% which overlaps with that of twice daily timolol. Timolol is approved for either once or twice daily use. The ocular hypotensive effect of latanoprost is approximately 27-30% on an average.[9] Patients who do not achieve target IOP levels with a single ocular hypotensive agent often are prescribed concomitant therapy with a medication that has a different mechanism of action.[10,11] In patients with POAG or OH whose IOP is not sufficiently controlled on timolol monotherapy, concomitant treatment with latanoprost has demonstrated additive IOP-reducing efficacy.[12,13]

To avoid the instillation of two drugs 3 or 4 times a day some fixed combinations have become available such as timolol-pilocarpine, timolol-dorzolamide and timolol-latanoprost.[8] The fixed combination of prostaglandin analog and beta-blocker is theoretically expected to provide better IOP lowering effect and fewer unwanted side effects than unfixed combination.[14-16] Fixed combination of latanoprost and timolol (LTFC) reduces instillation frequency of topical timolol to once daily and simultaneously minimize the washout effect and exposure to preservatives.[17]

However, there is a scarcity of research comparing the efficacy of the fixed and unfixed combinations of latanoprost and timolol in clinical practice for the management of open-angle glaucoma and OH. Therefore, the current study was undertaken to compare the efficacy of the fixed combination of latanoprost and timolol with that of the unfixed use of the individual components.

MATERIALS AND METHODS

A comparative randomized open-label trial was conducted for 1 year commencing from November, 2012. Newly diagnosed patients from ophthalmology department with open-angle glaucoma and OH were screened for this study. A total of 40 eligible patients (26 males and 14 females) suffering from POAG or OH after their informed consent were enrolled for the treatment after evaluating for inclusion and exclusion criteria. A total of 80 eyes were observed with a follow-up of 12 weeks. The study was approved by the Institutional Ethical Committee vide ref. no. Pharma/2012/2453 dated 07-11-2012.

Patients of either sex with age ≥18 years newly diagnosed with POAG or OH who were receiving either latanoprost 0.005% once daily or either timolol 0.5% once or twice daily in the preceding 4 weeks and whose IOP was not controlled with the prior monotherapy of latanoprost or timolol and remained ≥21 mmHg were included in the study.

Pregnancy/lactation, congestive heart failure, history of conduction defect or cardiogenic shock, heart block, angina, asthma/chronic obstructive pulmonary diseases, acute/uncontrolled medical or psychiatric illness, myasthenia gravis, ocular inflammation/ocular infection, normotensive glaucoma, acute angle closure glaucoma and patients with hypersensitivity to either of the two drugs were excluded from the current study.

Patients were randomized in equal numbers to two groups. They were assigned following medications for 12 weeks.

Group I: Fixed combination eye drops of latanoprost (0.005%) and timolol SR (0.5%), once a day, in the dose of 1 drop at 9 pm (LTFC).

Group II: Unfixed combination of latanoprost (0.005%), once a day in the dose of 1 drop at 9 pm and timolol SR (0.5%), once a day in the dose of 1 drop at 9 am (LTuFC).

Patients were evaluated at 0, 2, 4, 6 and 12 weeks for the assessment of (IOP) and visual acuity. IOP was recorded

Table 1: Post-treatment visual acuity in patients with POAG and OH

Visual acuity	Number of eyes (% age)		Statistical inference
	Group I (LTFC) (*n*=40)	Group II (LTuFC) (*n*=40)	
6/12 or better	8 (20)	14 (35)	*P*=0.133*; (Chi-square-test)
6/18-6/60 (low vision)	32 (80)	26 (65)	
Total	40 (100.00)	40 (100.00)	

POAG: Primary open-angle glaucoma, OH: Ocular hypertension, LTFC: Latanoprost/timolol fixed combination, LTuFC: Latanoprost/timolol fixed combination, *Non-significant (*P*>0.05)

with the help of non-contact tonometer and in visual acuity distant vision was assessed by Snellen's chart and near vision using reading test types of varying sizes, the notation being based on the printer "point" system. The data were analyzed with the help of computer software MS Excel and SPSS version 17.0 for Windows. Baseline comparability between the groups were evaluated using Chi-square/fisher's exact test and student's *t*-test. The outcome was reported as a mean±standard deviation with statistical significance assessed by unpaired Student's *t*-test. All analyses were carried out in accordance with intention to treat basis. A ($P < 0.05$) was considered statistically significant.

RESULTS

In the present study, patients presented with varied eye symptoms. Most of the patients had more than one symptom related to diseased eyes. The most common complaint was painless diminution of vision seen in 30 patients (65%) of both the treatment groups. There were other associated complaints like eye strain in 8 (20%) patients, followed by watering in the eyes and headache in 5 (12.50%) patients each, followed by scotomas in 4 (10%) patients as shown in Figure 1.

Both the groups LTFC (Group I) and LTuFC (Group II) caused a significant decline in IOP. Reduction in IOP was statistically highly significant ($P < 0.01$) at all the intervals in both the groups. On comparison, both the groups affected the IOP in a similar fashion and demonstrated no difference statistically as shown in Figures 2 and 3. Visual acuity did not alter statistically from baseline in either of the groups as well as demonstrated no difference statistically on the comparison ($P > 0.05$) as shown in Table 1 and Figure 4.

DISCUSSION

In this study, the fall in IOP in both groups fixed and unfixed was statistically significant at 2 weeks ($P < 0.01$) when compared with respective baselines and maximum reduction in IOP was observed at 12 weeks in both the groups. However, on comparison between the two groups there was no statistically significant difference ($P > 0.05$) thereby suggesting equal efficacy of both the groups in reducing IOP and thus failing to prove the superiority of the two groups over each other. This is in accordance to the previously published reports Diestelhorst et al.[18] and Zhao et al.[19] who revealed the similar efficacy of both the groups in reducing IOP. In addition, fixed combination was found to be non-inferior to the concomitant administration of both the drugs.

The rationale for using the latanoprost along with timolol has centered around the synergy that occurs as timolol works by decreasing the formation of aqueous humor in the ciliary epithelium whereas latanoprost acts via different mechanism,

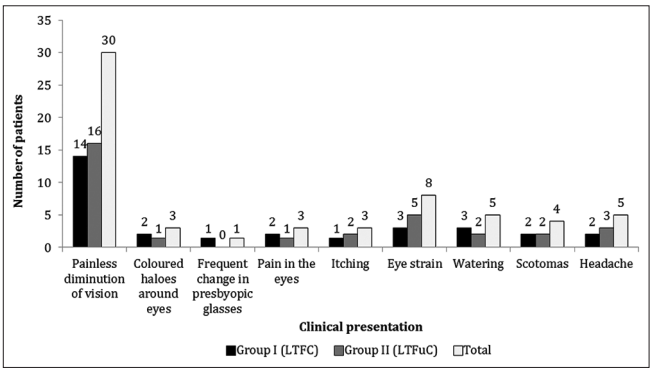

Figure 1: Bar chart showing clinical presentation of patients with primary open-angle glaucoma, ocular hypertension

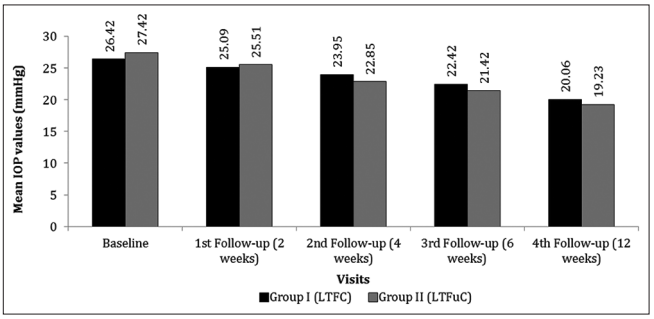

Figure 2: Bar chart showing mean intraocular pressure in Group I and Group II baseline and 2, 4, 6, and 12 weeks of follow-up

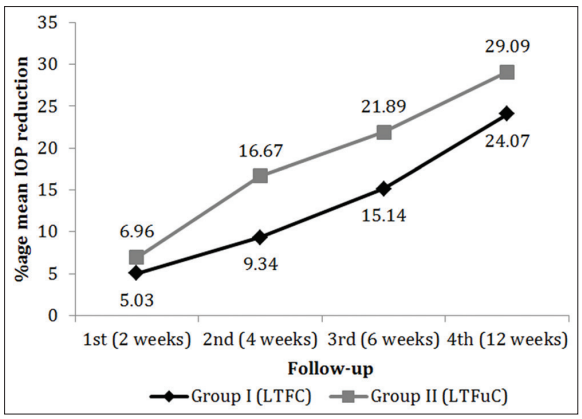

Figure 3: Line chart showing percentage mean intraocular pressure reduction in Group I and Group II from baseline

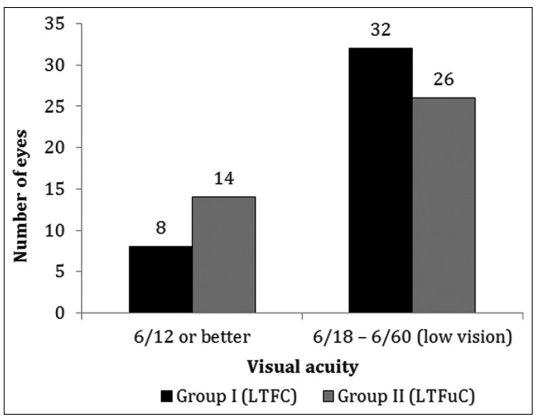

Figure 4: Bar chart showing post-treatment visual acuity in primary open-angle glaucoma, ocular hypertension

that is, by increasing the uveoscleral outflow as reported by Feldman.[20]

Fixed combinations of medications that lower IOP are increasingly used in the treatment of glaucoma and OH and offer potential advantages over combined use of the separate component medications including enhanced convenience, improved adherence, reduced exposure to preservatives, and possible cost savings as reviewed by Higginbotham 2010.[21] However, in the study by Mosavi et al.,[22] unfixed combination of latanoprost and timolol (LTuFC) was found to provide more IOP-lowering than fixed combination. The possible reasons for variation might be the inclusion of Malaysian population in the study, employing Goldmann applanation tonometry for measuring the IOP, longer duration of the study and sample size.

Furthermore, low IOP is associated with reduced progression of visual field defect as is reported in the advanced glaucoma intervention study 2000.[23] In this study, no significant change in visual acuity (i. e., upto two Snellen's line) in any treatment group was observed and there was no statistically significant difference in visual acuity in both the groups. However, two eyes in Group I and one eye in Group II showed deterioration of vision by one Snellen line at the end of the study period. This is in accordance to the previously published study by Siesky et al.[24] where the administration of latanoprost and timolol showed no significant effect on the visual acuity. However, no effect on visual function in the present study may be attributed to short-term comparison between the two treatments.

The current study suffers from few limitations. It was of short duration of 12 weeks only and with less sample size. Visual field and diurnal IOP assessments were not a part of the study which might have otherwise elaborated the observations as the study was done on an out-patient basis. In addition, no differentiation between POAG and OH was pre-specified in the present study as the aim was to observe the effects of both the treatment groups on IOP.

CONCLUSION

The conclusion drawn from the present study is that both the groups were well-tolerated, produced a significant reduction in IOP levels, effective in preventing the further deterioration of visual acuity but on direct comparison failed to prove superiority over each other in patients of POAG and OH. Thus, the clinicians have a wider choice of fixed or unfixed combinations of latanoprost and timolol, when monotherapy of either drug fails in the reduction of IOP and OH.

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