Content available at: https://www.ipinnovative.com/open-access-journals

IP International Journal of Ocular Oncology and Oculoplasty

Journal homepage: https://ijooo.org/

Original Research Article

Safety and efficacy of topical agents in primary open angle glaucoma- latanoprost versus combination of latanoprost & timolol maleate

Shilpi Agarwal[1], Sugyani Satapathy[2], Mukta Prasad[1,*]

[1]*Dept. of Ophthalmology, Patna Medical College, Patna, Bihar, India*
[2]*Dept. of Ophthalmology, Heritage Institute of Medical Sciences, Varanasi, Uttar Pradesh, India*

ARTICLE INFO

Article history:
Received 15-07-2021
Accepted 01-09-2021
Available online 25-10-2021

Keywords:
Prostaglandins
Glaucoma
Timolol
Beta adrenergic
Dual therapy

ABSTRACT

Aims: This prospective drug trial was done to compare latanoprost versus combination therapy of latanoprost and timolol maleate.
Methods and Materials: Patient were screened for primary open angle glaucoma and grouped as per pharmacological drugs used and measured IOP baseline before initiation of study. Group I consisting all patients with latanoprost monotherapy and Group II consisting of patients already using either latanoprost or timolol. Further A,B & C was assigned as per IOP baseline.
Results: In group I (Monotherapy), 28 patients were completed the follow up. The mean baseline IOP was 27.4 millimeter of Hg with standard deviation of 2.59. After 12 weeks of study, mean IOP was 19.66 millimeter of Hg with SD of 2.76. Mean IOP difference from baseline was 7.4 millimeter of Hg. So fall of 27.3% in IOP from pre-treatment level. In group II (Combination therapy), 19 patients were completed the follow up. The mean baseline IOP was 27.35 millimeter of Hg with standard deviation of 2.6. After 12 weeks of study mean IOP difference from baseline was 8.1 millimeter of Hg with SD of 2.0 millimeter of Hg i.e. a fall of 29.63% in IOP from pre-treatment level.
Conclusions: Combination therapy fared slightly better that Latanoprost alone in overall pressure reduction.

1. Introduction

Glaucoma is a group of disorder leading to progressive optic neuropathy with irreversible loss of vision with or without increase of IOP. As IOP is only modifiable risk factor, lowering it by medical &/or surgical technique is currently the mainstay of glaucoma treatment. The concept of "target IOP" was termed by American Academy of Ophthalmology as range of IOP adequate to stop progressive pressure-induced changes. 1 Efficacy of different pharmaceutical agents or combinations for lowering IOP, either by a percentage of baseline, or to a specified level is sole aim of treatment medically. The study is to evaluate the hypotensive effect of 0.005% Latanoprost as monotherapy in comparison to 0.005% Latanoprost with 0.5% Timolol maleate solution as combination therapy once daily.

2. Materials and Methods

Fifty seven consecutive patients were selected among the patients attending the outpatient department after they went through a detailed screening procedure. Detailed history of all cases followed by pre-randomization of cases acted as the baseline data for future follow up. Demographic information like age, sex and detail ocular and systemic medical history was noted. General and systemic examination was done. Visual acuity was assessed. Thorough ocular examination by Slit lamp

* *Corresponding author*.
E-mail address: drmukta98@gmail.com (M. Prasad).

https://doi.org/10.18231/j.ijooo.2021.059

bio-microscopy, dilated fundus examination with an indirect ophthalmoscope was done. Gonioscopy, intraocular pressure (IOP) measurement was also included. Iris colour, any ocular hypermia, presence of any aqueous cells or flare was noted. Clinical photography was taken for eyelash and iris colour. Fundus photograph was also taken.

After completing the general survey & ophthalmic examination; patient selection was done on the basis of clinical diagnosis of IOP more than 21 millimeter of Hg in either eye or visual acuity not less than 6/60. Patient's IOP was measured for at least 3 times preferable at 4 hours interval for getting a mean baseline whenever possible. After screening and considering all eligibility criteria, patients were divided into two groups:-

Group I- Patients having clinical diagnosis of IOP more than 21 millimeter of Hg in either eye were included. They were advised to use 0.005% Latanoprost eye drops once daily in the evening.

Group II- Patients on 0.5% timolol maleate or 0.005% latanoprost as monotherapy. Duration of therapy four weeks or more. IOP more the 21 millimeter of Hg.

Patients selected in each of the two groups were further subdivided into three groups (group A, B, C) according to their baseline (pre-treatment) IOP.

Group IA & IIA- patients having baseline IOP more than 21 millimeter of Hg but less than or equal to 25millimeter of Hg were kept in this subgroup.

Group IB &IIB – patients having baseline IOP more than 25 millimeter of Hg but less than or equal to 30 millimeter of Hg were kept in this subgroup.

Group IC and IIC – Patients having baseline IOP more than 30millimeter of Hg were kept in this subgroup.

All patients were instructed to immediately inform if any unusual reaction to study drugs developed. Group II patients were also advised to report urgently if any dyspnea or palpitation occurred particularly during the first few days of starting the drugs. The patients were advised to visit for follow up at 2^{nd}, 4^{th}, 8^{th} and 12^{th} week. IOP was recorded at 8 hourly intervals on 4 subsequent visits.

3. Results

The study was started with 57 patients. 34 patients were included in the group-I and 23 patients in group II. Four patients in group I and three patients in group II lost to follow up. Two patients of group I and one patient of group I, the treatment modality changed. Finally, 28 patients in group I and 19 patients in group II enlisted for final evaluation. Their effects were followed up for 12 weeks as per study design. Group IA, IB & IC patients received 0.005% Latanoprost once daily. Group IIA, IIB & IIC patients received 0.005% latanoprost with 0.5% timolol maleate once daily. There were 6 patients in Group IA, 17 patients in Group IB & five patients in Group IC. Three patients in Group IIA, 12 patients in Group IIB and 4 patients were in Group IIC.

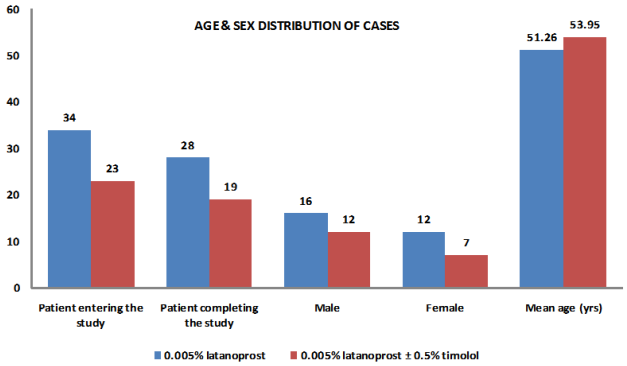

Fig. 1: Age and sex distribution of the cases

Group I patients treated with 0.005% latanoprost once daily. The pretreatment IOP in the group I was 27.04 millimeter of Hg with standard deviation (SD) of 2.59. In subgroup IA mean pretreatment IOP was 23.08+/- 0.81 millimeter of Hg in sub group IB it was 27.0 with SD of 1.35 and in subgroup IC it was 31.1with SD of 0.71 millimeter of Hg. At the end of 2^{nd} week or at 1^{st} visit the mean IOP in the group I was 25.36 millimeter of Hg standard deviation of ± 2.75. In subgroup IA mean IOP was19.8 ± 1.56 millimeter of Hg. in sub group IB it was 23.8 ± 1.88 and in subgroup IC it was 24.1 ± 0.67 millimeter of Hg. At the end of 4^{th} week or at 2nd visit the mean IOP in the Group I was 21.44 millimeter of Hg with standard deviation of 2.85. In subgroup IA, mean IOP was 17.6± 1.83 millimeter of Hg, in subgroup IB it was 21.8 ± 2.39 and in subgroup IC it was 24.9±1.23 millimeter of Hg. At the end of 8 week or at 3rd visit the mean IOP in the group I was 20.20±2.82 millimeter of Hg. In subgroup IA mean IOP was 16.8 ± 1.95 millimeter of Hg, in sub group I B it was 20.6 ± 2.81 and in subgroup IC it was 22.8 ± 1.72 millimeter of Hg. At the end of 12 week or at 4th Visit the mean IOP in the group I was19.66 ±2.76millimeter of Hg. In subgroup IA mean IOP was 16.3 ± 1.86 millimeter of Hg, in sub group IB it was 20.1 ± 2.15 and in subgroup IC it was 22.2 ± 1.72 millimeter of Hg.

Group II patients were treated with 0.005% latanoprost with 0.5% timolol maleate. The effect of latanoprost with timolol maleate in fixed combination was studied in 19 patients. The drug was administered once daily. The mean pretreatment IOP in the group II was 21.35 millimeter of Hg with standard deviation of ± 2.61. In subgroup IIA mean pretreatment IOP was 23.3 ± 0.97 millimeter of Hg, in sub group IIB it was 27.1 ± 1.17 and in subgroup IIC it was 31.1 ± 0.82 millimeter of Hg. At the end of 2^{nd} week or at 1^{st} visit the mean IOP in the group II was 23.77± 2.67 millimeter of Hg, in subgroup IIA mean IOP was 20.9 ± 1.78 millimeter of Hg, in sub group IIB it was 23.4 ± 2.14 and in subgroup IIC it was 27.1 ± 0.77 millimeter of Hg. At the end of 4^{th} week or at 2^{nd} visit the mean IOP in the group

II was 21.33 ±249millimeter of Hg, in subgroup IIA mean IOP was 19.4 ± 1.78 millimeter of Hg, in sub group IIB it was 20.8 ± 2.13 millimeter of Hg and in subgroup II C it was 24.3 ± 1.76 millimeter of Hg. At the end of 8^{th} week or at 3^{rd} Visit the mean IOP in the group II was 19.78 millimeter of Hg with standard deviation of ± 2.52, in subgroup IIA mean IOP was 18.4 ± 2.95 millimeter of Hg, in sub group IIB it was 19.4 ± 2.24 and in subgroup II C it was 22.1 ± 1.02 millimeter of Hg. At the end of 12th week or at 4^{th} visit the mean IOP in the group II was 19.24 millimeter of Hg with standard deviation of ±2.34., In subgroup IIA mean IOP was 17.8 ± 2.67 millimeter of Hg, in sub group IIB it was 18.8 ± 2.72 and in subgroup II C was 21.0 ± 1.15 millimeter of Hg. (Tables 1 and 2)

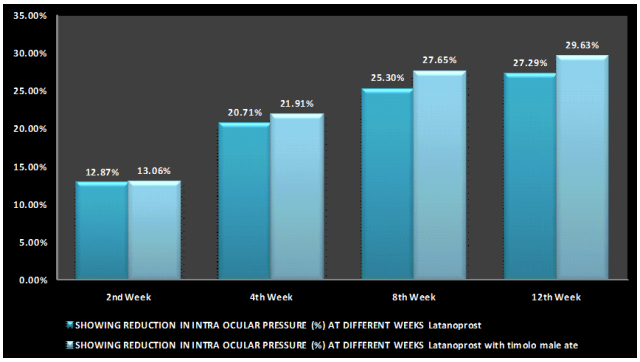

Fig. 2: Percentage reduction in IOP in different follow-up for group I & II

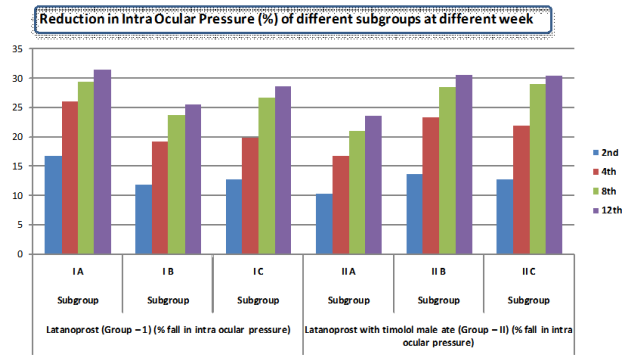

Fig. 3: Reduction in IOP in subgroups IA,IB,IC,IIA,IIB &IIC (%age)

Adverse effects of these drugs were charted which is summarized in the table.(Table 3)

4. Discussion

Medical management of primary open angle glaucoma requires thorough investigation, meticulous planning and lifelong frequent follow-up. The mainstay of the treatment is to lower intraocular pressure as close as possible to the target pressure, maintain it at this level and also prevent diurnal fluctuation. A combination of two or more drugs is common in the treatment of glaucoma. As a rule for greater efficacy a drug that increases outflow of aqueous humour such as latanoprost or Pilocarpine may be combined with a drug that reduces inflow such as beta adrenergic antagonist or carbonic anhydrase inhibitors.In present study, newly diagnosed patients with primary open angle glaucoma were treated with latanoprost once daily, while previously diagnosed but inadequately controlled IOP by either timolol or latanoprost were treated with latanoprost and timolol maleate in fixed combination once daily.

Similar results were found in previous several studies as in 6-weeks, double blind, randomized, multicenter study with 50 patients for study of effect of timolol alone, latanoprost alone and latanoprost with timolol maleate in fixed combination, researchers found that both latanoprost monotherapy and latanoprost with timolol maleate in fixed combination caused significant IOP reduction of 5.0 ±0.9 millimeter of Hg and 5.0 ±0.9 millimeter of Hg respectively.[1,2] The efficiency and safety of latanoprost with timolol maleate in fixed combination administered once daily versus monotherapy with either latanoprost once daily or timolol twice daily. After 26 weeks, they found that in the fixed combination therapy group mean IOP was 199 ± 3.4 millimeter of Hg and in latanoprost treated patient it was 20.8 ± 4.6 millimeter of Hg and well-tolerated.[3] Result of present study corresponds with the study of Higginbotham and others in IOP reduction effect of both group I and group II drugs. However because in the present study there was no randomization among group I and group II cases, and also the baseline IOP of group II is incomparable with that of group I cases, results of IOP reduction effects of two groups are statistically incomparable. In open label, prospective multicenter Indian study of latanoprost in cases of primary open angle glaucoma and ocular hypertension by Agrawal A and other the baseline mean IOP was found 27.1 ±6.0 millimeter of Hg and after 12 weeks, the mean IOP reduced by 9.1±3.9 mg Hg (33.6%) from the baseline (P<0.05).[4]

Result of group I case of present study (7.4 ±2.76 millimeter of Hg, 27.3%) is nearly similar to the above study. Present study showed results consistent with several other past studies. Mishima et al found latanoprost reduced IOP in primary open angle glaucoma and ocular hypertension after 12 weeks by 6.2±2.7 millimeter of Hg (26.8%).[5] Camras et al found latanoprost reduced IOP after 6 months by 6.7±4.6 millimeter of Hg (27%).[6] O'Donghue et al found latanoprost reduced IOP after 3 months by 8.5 ±3.3 millimeter of Hg (32%).[7] Nepalia LK et al found that after 12 weeks latanoprost treated patients showed IOP reduction of 11.46 ±0.36 millimeter of Hg (43.62%) (P<0.001).[8] Watson et al found latanoprost significantly reduced IOP by approximately 8 millimeter of Hg from baseline value.[9] On the basis of criteria defining successful

Table 1: Showing mean iop at different weeks (Mean ± S.D)

Week	0.005% latanoprost (n=28)		0.005% Latanoprost with 0.5% timolol maleate (n = 19)
	Mean IOP (millimeter of Hg)	p Value	Mean IOP (millimeter of Hg)
Pretreatment	27.04±2.59	<0.001	27.35±2.61
2^{nd} Week	23.56±2.74	<0.001	23.77±2.67
4^{th} Week	21.44±2.85	<0.001	21.33±2.49
8^{th} Week	20.20±2.82	<0.001	19.78±2.59
12^{th} Week	19.66±2.76	<0.001	19.24±2.54

Table 2: Intra ocular pressure (subgrroups) at different weeks (Mean ± S.D)

Week	0.005% latanoprost (n=28)			0.005% Latanoprost with 0.5% timolol maleate (n = 19)		
	Group I- IOP (mmHg) > 21.0 to 25.0	Group IB-IOP (mmHg) > 25.0 to 30.0	Group IC-IOP (mmHg)>30.0	Group IIAIOP (mmHg) > 21.0 to 25.0	Group IIBIOP (mmHg) > 25.0 to 30.0	Group IICIOP (mmHg)>30.0
Pretreatment	23.8±0.81	27.0±1.35	31.1±0.71	23.3±0.97	27.1±1.17	31.1 ± 0.82
2^{nd} Week	19.8±1.56	23.6±1.88	27.1±0.67	20.9±1.78	23.4±2.14	27.1 ± 0.77
4^{th} Week	17.6±1.83	21.8±2.39	24.9±1.23	19.4±1.78	20.8±2.13	24.3 ± 1.76
8^{th} Week	16.8±1.95	20.6±2.81	22.8±1.75	18.4±2.95	19.4±2.24	22.1 ± 1.02
12^{th} Week	16.3±1.86	20.1±2.15	22.2±1.72	17.8±2.67	18.8±2.72	21.0 ± 1.15

Table 3: Adverse effects of 0.005% latanoprost and 0.005% tretment with timolol maleate and its distribution

Adverse effects	0.005% Latanoprost (n=28)	0.005% Latanoprost with 0.5% Timolol maleate (n=19)	Total (n=47)
Conjunctival congestion	1 (3.57%)	1 (5.3%)	2 (4.3%)
Itching	1 (3.57%)	2(10.5%)	3 (6.4%)
Watering	1 (3.57%)	0	1 (2.1%)
Episcleritis	0	1 (5.3%)	1 (2.1%)
Swelling of lid	0	0	0
Eyelashes lengthening	0	0	0
Superficial punctuate keratitis	0	0	0
Iris pigmentation	0	0	0
Crystoid macular oedema	0	0	0
Systemic adverse effects	0	0	0

outcome at final IOP less than or equal to 21 millimeter of Hg or decrease in IOP of 20% or more from the baseline, drugs used in both the group seemed to be effective.14% of cases of group I and 94.7% of cases of group II resulted in successful outcome after 12 weeks of therapy. In Indian latanoprost study, the IOP lowering effect and safety profile Latanoprost were studied for 3 months on 126 patient with primary open angle glaucoma and ocular hypertension. They found total 20 (16.8%) adverse events, which included both ocular and systemic events. The most common ocular events were mild congestion (4.2%). itching (2.5%) dryness of the eye (1.7%), watering and mild discharge (1.75) and eye pain (1.796). No systemic adverse event was found. Nepalia LK et al found that latanoprost treated patients were showed only mild and transient ocular side effects like mild conjunctival hyperemia and blurred vision.[8] Present study corresponds with above studies, out of 47 cases of both group 7 (14.9%) adverse events reported itching in 3 (6.4%) cases, mild congestion in 2 (4.3%) watering in 1 (2.1%) of cases, No systemic side effects were reported. Although, Mc Mohan et al (1979) in their study of timolol on 165 patients reported adverse events involving one or more organ system in 38 (91%) patient and 15 (9%) patients were discontinued from the study, group - II cases of present study not showed any systemic or any severe ocular adverse effect.[10] No case of present study was withdrawn from the study due to adverse events. Timolol was given one daily in fixed combination with latanoprost. During patient selection, those patients presenting with signs or symptoms of cardiovascular disease or chronic pulmonary obstructive disease were excluded from the study.

5. Conclusion

Various pharmacological agents are being used to maintain IOP in open angle glaucoma. Combination therapy ensures consistence of results & safety profile in comparison to monotherapy. Those resistant cases not responding to monotherapy have more therapeutic benefits from dual therapy of latanoprost and timolol fixed combinations. Many newer agents are being researched which can ensure better results but cost effectiveness in developing country is necessary.

6. Acknowledgement

None.

7. Conflict of Interest

The authors declare that there are no conflicts of interest in this paper.

8. Source of Funding

None.

References

1. American Academy of Ophthalmology. Primary Open-Angle Glaucoma. Preferred Practice Pattern. San Francisco, CA: American Academy of Ophthalmology; 2010.
2. Franks WA, Renard JP, Cunliffe IA, Rojanapongpun P. A 6-week, double-masked, parallel-group study of the efficacy and safety of travoprost 0.004% compared with latanoprost 0:005%/timolol 0.5% in patients with primary open-angle glaucoma or ocular hypertension. *Clin Ther*. 2006;28(3):332–9. doi:10.1016/j.clinthera.2006.03.001.
3. Higginbotham EJ, Olander KW, Kim EE, Grunden JW, Kwok KK, Tressler CS. United States Fixed-Combination Study Group. Fixed combination of latanoprost and timolol vs individual components for primary open-angle glaucoma or ocular hypertension: a randomized, double-masked study. *Arch Ophthalmol*. 2010;128(2):165–72. doi:10.1001/archophthalmol.2009.384.
4. Agarwal A, Agarwala N, Chandra R, Dhami G, Dhesi R, Kendra P, et al.. Open Label, Prospective, Multicentre Indian Study of Latanoprost in Primary Open Angle Glaucoma and Ocular Hypertension; 2002.
5. Mishima HK, Masuda K, Kitazawa Y, Azuma I, Araie M. A comparison of latanoprost and timolol in primary open-angle glaucoma and ocular hypertension. A 12-week study. *Arch Ophthalmol*. 1996;114(8):929–32. doi:10.1001/archopht.1996.01100140137004.
6. Camras CB, Alm A, Watson P, Stjernschantz J. Latanoprost, a prostaglandin analog, for glaucoma therapy. Efficacy and safety after 1 year of treatment in 198 patients. Latanoprost Study Groups. *Ophthalmology*. 1996;103(11):1916–24. doi:10.1016/s0161-6420(96)30407-7.
7. O'donoghue EP. A comparison of latanoprost and dorzolamide in patients with glaucoma and ocular hypertension: a 3 month, randomised study. Ireland Latanoprost Study Group. *Br J Ophthalmol*. 2000;84(6):579–82. doi:10.1136/bjo.84.6.579.
8. Nepalia LK. Comparison of latanoprost and timolol in primary open angle glaucoma and ocular hypertension 63rd AIOS conference; 2005.
9. Watson P, Stjernschantz J. A six-month, randomized, double-masked study comparing latanoprost with timolol in open-angle glaucoma and ocular hypertension. The Latanoprost Study Group. *Ophthalmology*. 1996;103(1):126–37. doi:10.1016/s0161-6420(96)30750-1.
10. Mcmahon CD, Shaffer RN, Hoskins HD, Hetherington J. Adverse effects experienced by patients taking timolol. *Am J Ophthalmol*. 1979;88(4):736–8. doi:10.1016/0002-9394(79)90674-3.

Author biography

Shilpi Agarwal, Senior Resident

Sugyani Satapathy, Senior Resident

Mukta Prasad, Senior Resident

Cite this article: Agarwal S, Satapathy S, Prasad M. Safety and efficacy of topical agents in primary open angle glaucoma- latanoprost versus combination of latanoprost & timolol maleate. *IP Int J Ocul Oncol Oculoplasty* 2021;7(3):289-293.