

## Comparative Effect of Latanoprost/Timolol Fixed Combination and Unfixed Combination in Patients with Ocular Hypertension Attending Irrua Specialist Teaching Hospital, Irrua, Nigeria

<sup>1</sup>Ovienria W. A., <sup>1</sup>Enock M. E., <sup>2</sup>Akpamu U., <sup>3</sup>Akhideno P.E., <sup>1</sup>Momoh N.

<sup>1</sup>Department of Ophthalmology, Irrua Specialist Teaching Hospital, Irrua, Edo State, Nigeria.

<sup>2</sup>Department of Physiology, Faculty of Basic Medical Sciences, College of Medicine, Ambrose Alli University, Ekpoma, Edo State, Nigeria.

<sup>3</sup>Department of Internal Medicine, Irrua Specialist Teaching Hospital, Irrua, Edo State, Nigeria.

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**Abstract:** Studies comparing the effect of fixed and unfixed combination of latanoprost and timolol are limited globally and nearly absent among the Nigerian population. This study therefore compares the effect of fixed and unfixed combination of latanoprost and timolol on intraocular hypertension among Nigerian population. The study was a randomized control trial consisting of 102 patients with ocular hypertension who received latanoprost/timolol fixed combination (n=48) and latanoprost/timolol unfixed combination (n=54) for medical reasons. Follow-up visits over 30 weeks was scheduled for 2 weeks from entry date and thereafter every 4 weeks for the remaining 28 weeks making a total of 9 clinic visitations. During the period of the study, the ophthalmologists followed usual care routines and intraocular pressures were recorded while also observing adverse events and evaluating efficacy, safety, tolerability and compliance. Overall, there was 47.73% reduction of intraocular pressure with fixed combination of latanoprost/timolol as against 43.26% reduction with unfixed combination. The greatest reduction impacts were observed two weeks after commencing treatment (-8.27mmHg and -5.74mmHg for fixed and unfixed combinations respectively) and then efficacy reduces progressively for both drugs. This study showed that latanoprost and timolol combinations are effective for intraocular hypertension. However, fixed combination was observed to be more effective compared to unfixed combination at least among Nigerian population.

**Keywords:** Latanoprost; Timolol; Fixed combination; Unfixed combination; Nigerian.

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### I. Introduction

For over 3 decades timolol has been the most popular, effective aqueous suppressant and has been regarded as “gold standard” drug for comparison with other intraocular hypotensive drugs. While it is accepted that pressure less than 18mmHg retard the progression of glaucoma [1,2], 1mmHg extra reduction in intraocular pressure in advanced glaucoma is clinically meaningful. In this regards, prostaglandin analog such as latanoprost was demonstrated to be more effective in reducing intraocular pressure. In fact, our previous finding justifies this fact among Nigerian population inhabiting the South-South geo-political zones and environs [3].

Of interest is the report that mono-therapy with topical pressure lowering drugs is often inadequate to achieve target pressure in most patients [4,5] and thus, the promotion of combinations of two or more intraocular pressure lowering drugs. The first attempt on combination therapy was timolol and pilocarpine that successfully reduced the frequency of pilocarpine instillation without affecting its effectiveness [6]. In ocular hypertension where ocular hypotensive monotherapy do not results to target intraocular pressure (IOP) level, adding a second medication when the original agent showed some effectiveness was recommended [7]. For this reason, Timolol has been combined with various other pressure lowering drugs including prostaglandin analog. While ineffective pressure lowering effect has been reported for some combination treatments [8], adjunctive therapy of latanoprost and timolol has been shown to provide pressure reduction as compared to monotherapy of the individual drug [9,10].

Of interest in the present study are latanoprost, a prostaglandin F2a analogue that acts by increasing outflow [11,12], and timolol, a beta-adrenergic receptor antagonist that acts by reducing aqueous humor production [13,14]. The combination of these two IOP lowering agents has been shown to have an additive effect [9,10,15,16]. To the best of our knowledge, there is no available report on the effectiveness of fixed or unfixed combinations of timolol and latanoprost in Nigerian population. Moreover, there is paucity of studies comparing the effect of fixed and unfixed combination of latanoprost and timolol. Thus, this study is aimed at comparing the pressure lowering effect of fixed and unfixed combination of latanoprost and timolol in the Nigerian population.

## II. Materials And Methods

**2.1. Drug of study:** Timolol is a systemic beta-blockers acting as ocular hypotensive by decreasing aqueous secretion. It is the most used topical anti-glaucoma medication, highly available, affordable, and relatively good compliance as it is almost free of ocular side effects. On the other hand, latanoprost is a prostaglandin analogue and act by lowering IOP by increasing uveoscleral aqueous outflow. It is relatively a new class of anti-glaucoma drug with minimal systemic side effects but is expensive especially with reference to economic status of Nigerian inhabitance.

Fixed combination of latanoprost/timolol containing 50mg of latanoprost and 6.83mg of timolol maleate in same single bottle was given once daily. While the unfixed combinations of latanoprost(0.005%) and timolol were both on separate bottles and were taken once daily for latanoprost and twice daily for timolol maleate.

**2.2. Study area:** The study was a randomized controlled trial study conducted in the Ophthalmic Clinic of Irrua Specialist Teaching Hospital, Irrua, Edo State, South-South, Nigeria. The study was conducted between January 2014 and December 2014.

**2.3. Inclusion criteria:** Ages between 10 and 80 years, both sexes, no inflammation or rubeotic glaucoma, not allergic to either of the medications, no noticeable or documented side effect to the drug of study. However, patients who are ages <10 or >80 years, IOP <21 or >50 mmHg, any form of surgical intervention, known allergies, requiring other IOP lowering modalities, existing infection or inflammation were excluded. In addition, patients who missed more than 2 clinic visits were also excluded.

**2.4. Methods:** Once a patient was identified as suitable, the study was explained to the patient and consent to be included in the study obtained. The study was explained to the patients and they were told they can decline and decide to be excluded from the study at any point in time without consequence on the services they received from the clinic.

Before commencement of therapy, patients' initial IOP were measured (Goldmann's applanation tonometer) and recorded. This served as the control (baseline) value. Group A was placed on timolol maleate ophthalmic solution (0.5%) applied one drop into the lower fornix of each eye at 12-hourly interval. Group B was on latanoprost ophthalmic solution (0.005%) applied one drop into the lower fornix of each eye once daily (at night). Patients were enrolled over a period of 12 weeks in the regular clinic setting. Patients for the study were followed-up in 8 clinic visits over a 30 week period. During these periods, their IOP were measured on a two week basis between the hours of 9.00am and 11.00am to take into consideration the diurnal variations of IOP. IOP was measured and recorded during each clinic visit.

**2.5. Analysis:** SPSS (16.0 Version) was used for data entry and analysis. The descriptive statistics conducted and presented in suitable table.

## III. Results

The results are as presented in table 1, 2 and 3. There was no recorded adverse effect in the study subjects that were treated on the combinations used in this study. Table 1 shows the impact of unfixed combination of latanoprost/timolol on IOP for the period of 30 weeks. IOP was observed to reduce progressively with the administration of unfixed combination of latanoprost/timolol. Similarly, table 2 shows the impact of fixed combination of latanoprost/timolol on IOP for a period of 30 weeks. Fixed combination of latanoprost/timolol was observed to bring about a progressive reduction in IOP.

Table 3 is a comparative reduction potential of unfixed and fixed combination of latanoprost/timolol on IOP for the duration of the study. For the study period, unfixed combination latanoprost/timolol resulted in 11.60mmHg reduction in IOP while fixed combination resulted in a 14.10mmHg in IOP. Comparatively, this is 43.26% reduction for unfixed combination as against 47.73% reduction for fixed combination. IOPs were observed to drop by -5.74mmHg for unfixed combination and -8.27mmHg for fixed combination in the first two weeks of treatment and the reducing impact reduces for both treatments as the duration of treatment progresses. Overall, for the 30 weeks period there was about 4.47% difference between fixed and unfixed combinations of latanoprost/timolol. This indicates that fixed combination is 10.33% more potent than unfixed combination.

**Table 1: IOP at Entry and Pattern of Impact of Unfixed Combination of Latanoprost/Timolol**

	Entry	2wks	6wks	10wks	14wks	18wks	22wks	26wks	30wks
Valid Number of Patients	54	54	54	54	54	54	54	54	54
Missing	0	0	0	0	0	0	0	0	0
Mean IOP	26.80	21.06	19.13	18.09	17.20	16.31	15.87	15.46	15.20

**Table 2:** IOP at Entry and Pattern of Impact of Fixed Combination of Latanoprost/Timolol

	Entry	2wks	6wks	10wks	14wks	18wks	22wks	26wks	30wks
Valid Number of Patients	48	48	48	48	48	48	48	46	48
Missing	0	0	0	0	0	0	0	2	0
Mean IOP	29.54	21.27	19.19	17.62	16.96	16.27	15.73	15.52	15.44

**Table 3:** Comparative Reduction Potential of Unfixed and Fixed Combination of Latanoprost/Timolol on IOP

WEEKS	Unfixed combination (latanoprost/timolol in Separate Bottles) (IOP in mmHg)	Fixed combination (latanoprost/timolol in same bottle) (IOP in mmHg)
2wks	5.74	8.27
6wks	1.93	2.08
10wks	1.04	1.56
14wks	0.89	0.67
18wks	0.89	0.69
22wks	0.44	0.54
26wks	0.41	0.21
30wks	0.26	0.08
TOTAL	11.60 (43.26%)	14.10 (47.73%)

#### IV. Discussion

This study showed that the combinations of latanoprost/timolol are effective and well tolerated. This is evident in the observed IOP lowering effect and unrecorded adverse outcomes in our study population. This finding is in accordance with the reports of several prospective and randomized clinical trials where the combinations of latanoprost/timolol have demonstrated effectiveness and tolerability [17-23].

The findings of this study showed that combinations of latanoprost and timolol have a reducing effect on IOP. Comparatively however, fixed combination of latanoprost/timolol has greater impact than unfixed combination. This finding correlates with the theoretical reported by Shin et al.[22], Higginbotham et al.[21] and Pfeiffer[23] that fixed combination of prostaglandin analog and beta blocker is expected to provide better pressure lowering effect than unfixed combination. This theoretical report was said to indirectly improve the quality of life of glaucoma patients [24,25]. On the contrary, the present finding disagrees with the study by van der Valk et al. [26] who found unfixed combination of latanoprost and timolol to provide better pressure lowering effect compared to fixed combination.

In the present study, fixed combination of latanoprost/timolol was found to have 10.33% IOP reducing potential than unfixed combination. In glaucoma or ocular hypertension individuals, a fixed-combination formulation was said to be preferred to multidrug regimens in order to maximize patient compliance and quality of life [7]. This may be the reason why fixed combination of latanoprost/timolol showed better reducing IOP capacity compared to unfixed combination where individuals were expected to take from different bottles and twice daily. This assertion is based on the fact that when two drugs are required to control IOP, there are a number of potential advantages to using a fixed combination and this was said to include absence of risk of drug washout[27], reduced exposure to preservatives, and ultimately better patient compliance and quality of life[28].

While it has been suggested that patients with high IOP should use more than one ocular hypotensive therapy to reduce IOPs to levels that may be expected to slow or stop disease progression [5], this present study supports the combination of fixed IOP hypotensive therapy. Although both fixed and unfixed combinations of ocular hypotensive drugs resulted in similar IOP at the end of 30 weeks, if greater impact is needed in two weeks it is recommended that fixed combination be utilized.

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