

IS LONG TERM DRIFT A DETERMINING FACTOR IN PRIMARY OPEN ANGLE
GLAUCOMA WHEN COMPARING TIMOLOL TO LATANOPROST?

by

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ABSTRACT

Objective: To compare the change over time of intra-ocular pressure (IOP) lowering effects of timolol maleate to latanoprost in 115 eyes. *Methods:* In a multi-center, retrospective analysis, 22.5 (45 eyes) patients with primary open-angle glaucoma (POAG) were treated with timolol and 35 (70 eyes) patients were treated with latanoprost. Patients with a baseline IOP of greater than 35mmHg or those with advanced glaucoma (cup to disc ratios of .9/.9 or greater and/or visual field loss within 10 degrees of fixation in one or more quadrants) were excluded. IOP measurements were obtained using Goldmann applanation tonometry. In each treatment group mean IOP readings were calculated. Distributions of slopes for IOP over time were compared between treatment groups. *Results:* Of the 115 eyes, 45 were treated with timolol and 70 were treated with latanoprost. The mean pre-treatment IOP was 20 +/- 4.85 for timolol and 22 +/-6.0, which decreased by 6 mmHg and 6 mmHg with timolol and latanoprost, respectively. Of 45 eyes treated with timolol 0/45 showed long-term drift, as defined by an increase in IOP of 5mmHg or more. In 70 eyes treated with latanoprost, long-term drift was demonstrated in 9/70 eyes. *Conclusion:* A diminished IOP lowering effect was not measured in patients using timolol compared to latanoprost over a 12-month period.

TABLE OF CONTENTS

	Page
LIST OF TABLES.....	v
LIST OF FIGURES.....	vi
INTRODUCTION.....	1
METHODS.....	3
RESULTS.....	4-7
DISCUSSION.....	7,8
REFERENCES.....	9

LIST OF TABLES

Table	Page
1 Average decrease in Intraocular pressure over one year.....	6

LIST OF FIGURES

Figure		Page
1	Number of eyes represented in study.....	4
2	Decrease in IOP in patients using timolol.....	4
3	Decrease in IOP in patients using latanoprost.....	5
4	Comparison of IOP-lowering effects of timolol v. latanoprost.....	6
5	Bar graph depiction of IOP decrease using timolol v. latanoprost....	7

INTRODUCTION

Glaucoma is the cause of blindness in over 6.7 million people worldwide.^{1,2} In the United States, glaucoma is the leading cause of legal blindness.³ Because open angle glaucoma occurs asymptotically it often goes undiagnosed in millions of people. The initial intervention in glaucoma therapy involves the reduction of intra-ocular pressure with the use of topical therapy.

The first line therapy for the initial lowering of intra-ocular pressure in primary open angle glaucoma has been the use of beta-blockers, particularly, Timolol maleate 0.5%.² More recently, however, prostaglandin analogs have replaced the beta-blockers as an effective first line therapy in POAG treatment. The mechanism of action by which these two drugs effect intraocular pressure differs, and often they are used in conjunction to cause a synergistic effect on lowering IOP.

The mechanism of action of beta-blockers in the reduction of intraocular pressure involves antagonism of beta2-adrenoceptor at the ciliary body.² Its sympathomimetic activity causes a mean decrease in IOP by 30% and higher.⁴ When used in the treatment of only one eye, beta-blockers have been known to cause a consensual decrease in IOP in the fellow eye, as well.²

The ocular side effects of timolol are generally mild and well tolerated by most patients. Some of these effects include stinging upon instillation, dry eye secondary to reduced tear break-up time, and corneal anesthesia. Other more severe complications include superficial punctate keratitis and corneal erosions.^{2,4}

The use of topical beta-blockers also may produce systemic side effects. Some of these may be more severe than others and include bradycardia, hypotension, shortness of breath, diarrhea, and depression.⁴ Non-selective beta-blockers, such as Timolol, are contraindicated in patients with asthma because they are known to cause bronchospasm,

wheezing and dyspnea. Timolol elicits an adverse reaction in patients with chronic obstructive pulmonary disease and those with cardiac failure, and is therefore contraindicated in these patients.² Beta-blockers are also known to cause an increase in low density lipids.⁵

A newer line of therapy, the prostaglandin analogs, are believed to be at least as effective as the beta-blockers in the reduction of IOP and cause less adverse effects. Prostaglandin analogs such as Latanoprost, are selective antagonists of the FP receptors present in the eye.² The mechanism of their action is through an increase of uveoscleral outflow by remodeling the extracellular matrix adjacent to the ciliary muscle. Prostaglandins reduce collagen levels in the ciliary muscle and adjacent sclera, therefore reducing hydraulic resistance to the aqueous outflow through these tissues.²

The reported side effects of prostaglandin analogs include darkening of the iris in light irides as soon as 4 weeks after initial therapy, increased pigmentation of eyelid skin and hypertrichosis. Latanoprost has also been known to produce conjunctival hyperemia in about one third of patients.^{2,4} The most significant side effect associated with prostaglandin analogs is an inflammatory response in the eye. Therefore, their use is contraindicated in patients undergoing cataract surgery, those with a history of herpes simplex keratitis, or those with a history of anterior uveitis.² Unlike Timolol, Latanoprost is safe to use in asthmatic patients because it does not cause bronchospasm.

Many optometrists and ophthalmologists are now replacing beta-blockers with prostaglandin analogs as the first line of therapy for POAG. Although there has been a great deal of research comparing the efficacy of these drops, there has been no consensus on the “long-term drift,” or diminished effectiveness of these drops with long-term treatment.⁶ This study presents a detailed analysis of the IOP reducing effects of these two topical glaucoma treatments over a 12-month period.

SUBJECTS AND METHODS

The study was designed as a randomized retrospective analysis comparing topical timolol and topical latanoprost in patients with POAG. Patient records included in the study were selected from Battle Creek Veterans Administration Medical Center, Battle Creek, MI, John D. Dingell Veterans Administration Medical Center, Detroit, MI, and Shelby Eye Care, Shelby Township, MI. Patient selection primarily included previously diagnosed POAG with few newly diagnosed subjects. The majority of subjects showed minimal to no glaucomatous visual field loss. Among the patients who had been previously treated the interval between study inclusion and prior treatment ranged between 1-5 years, with the exception of two patients whose initial treatment was 8 years prior.

Exclusion criteria included prior ocular surgical intervention for control of IOP and any condition preventing reliable Goldmann applanation tonometry measurements. Patients with a baseline IOP of greater than 35mmHg or those with advanced glaucoma (cup to disc ratios of .9/.9 or greater and/or visual field loss within 10 degrees of fixation in one or more quadrants) were also excluded.

IOP readings were measured using Goldmann Applanation Tonometry. Pre-treatment pressures were compared to mean IOP lowering effects after initiation of topical therapy with either timolol or latanoprost. IOP measurements included pre-treatment readings, 4-6 weeks post-treatment, and 12 months post-treatment. The mean change in pressure was calculated for each treatment group. The efficacy of the two drugs was evaluated based on initial mean IOP lowering effects and those measured at 1 year.

RESULTS

In all, 115 eyes were used in our study, 45 treated with timolol and 70 treated with latanoprost (figure 1).

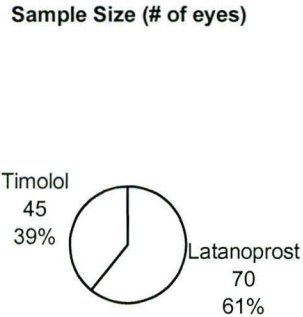


Figure 1. Number of eyes represented in study.

The results of IOP reduction in eyes treated with timolol showed a weak negative correlation. There was, in fact, a positive decrease in IOP in timolol treated eyes over the span of 4-6 weeks and 12-14 months. There were very few outliers depicted in figure 2, which illustrates the consistency of the pressure lowering effect of timolol.

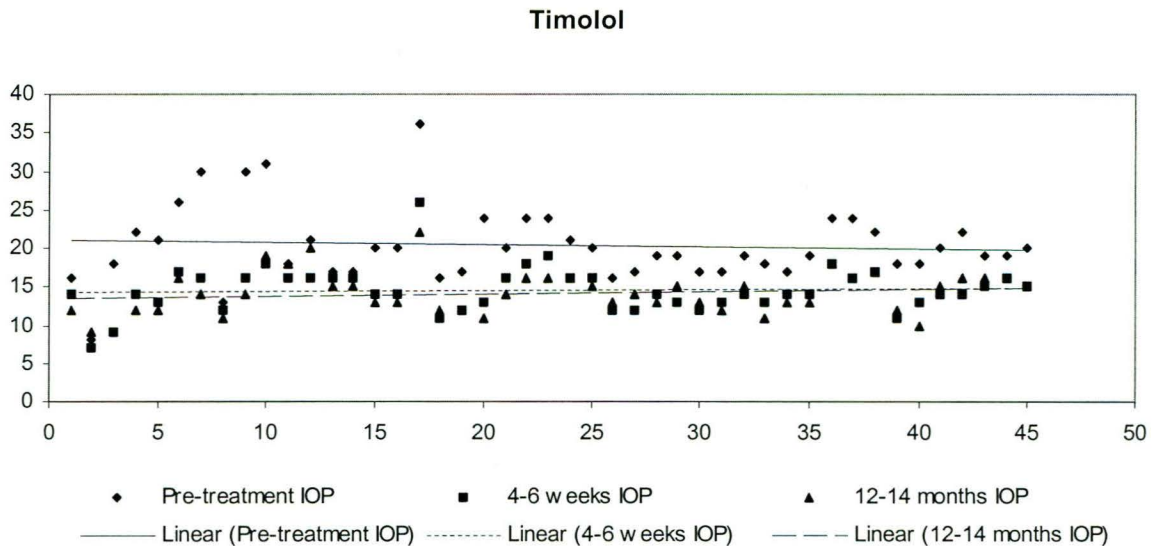


Figure 2. The scatter-plot above shows the amount of decrease in intraocular pressure from baseline to 4-6 weeks and 12-14 months post-treatment, respectively, in patients using timolol.

The results of IOP reduction in eyes treated with latanoprost showed a weak negative correlation. There was, in fact, a positive decrease in IOP in latanoprost treated eyes over the span of 4-6 weeks and 12-14 months. There were more outliers when compared with timolol treated eyes, illustrating less consistency in the IOP reducing effects of latanoprost. However, a positive reduction in pressure is apparent.

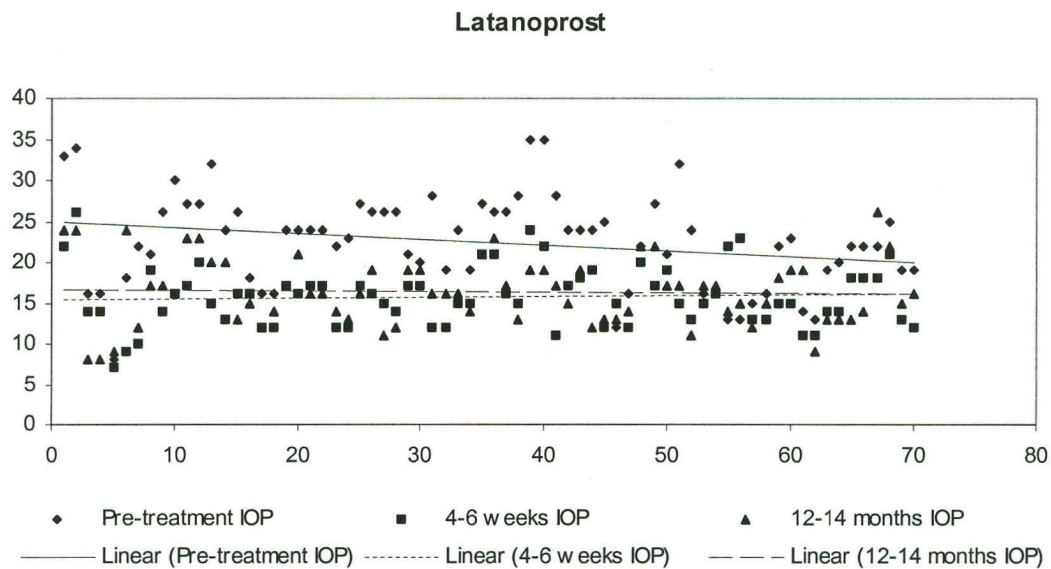


Figure 3. The scatter-plot above shows the amount of decrease in Intraocular pressure from baseline to 4-6 weeks and 12-14 months post-treatment respectively, using latanoprost.

The mean (\pm -SD) of the daily IOP levels at baseline were 20 ± 4.85 in the timolol group and 22 ± 6 in the latanoprost group. At 4-6 weeks the corresponding levels were 15 ± 2.96 mmHg versus 16 ± 4 mmHg, respectively. Reduction from baseline was roughly equal between the timolol (6 ± 3.82) and latanoprost (6 ± 5.25) groups (figure 4).

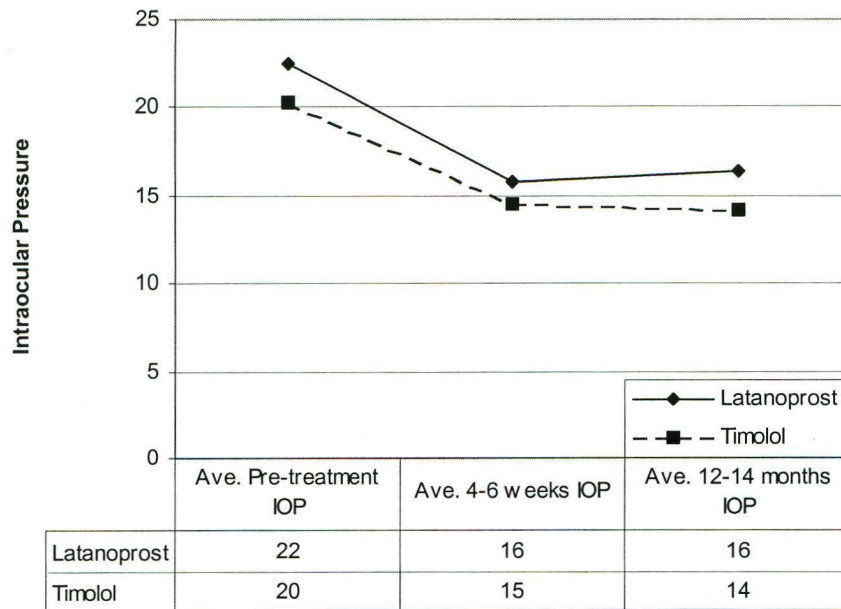


Figure 4. A comparison between the pressure lowering effects of latanoprost vs. timolol.

At the end of the 12-month study, the measured drop in IOP for the timolol group was 6 ± 3.82 and 6 ± 5.25 for those treated with latanoprost. Therefore, at the end of 1 year, timolol demonstrated a 30 % drop in IOP, while latanoprost decreased IOP by 27 %. (Table 1)

Sample Size (# of eyes)	Treatment	Ave. Pre-treatment IOP	Ave. 4-6 weeks IOP	Ave. 12-14 months IOP	% Decrease 4-6 weeks IOP	% Decrease 12-14 months IOP	% Difference 4-6 weeks IOP and 12-14 months IOP
70	Latanoprost	22	16	16	30%	27%	3%
45	Timolol	20	15	14	28%	30%	-2%

Table 1. A representation of the average decrease in pressure over the course of a year in eyes treated with latanoprost vs. timolol. Also note the increased effectivity of timolol vs. latanoprost between 4-6 weeks and 12-14 weeks of treatment.

Below is an illustration showing the 4-6 week and 12-14 month reduction in IOP of latanoprost and timolol treated eyes described in Table 1.

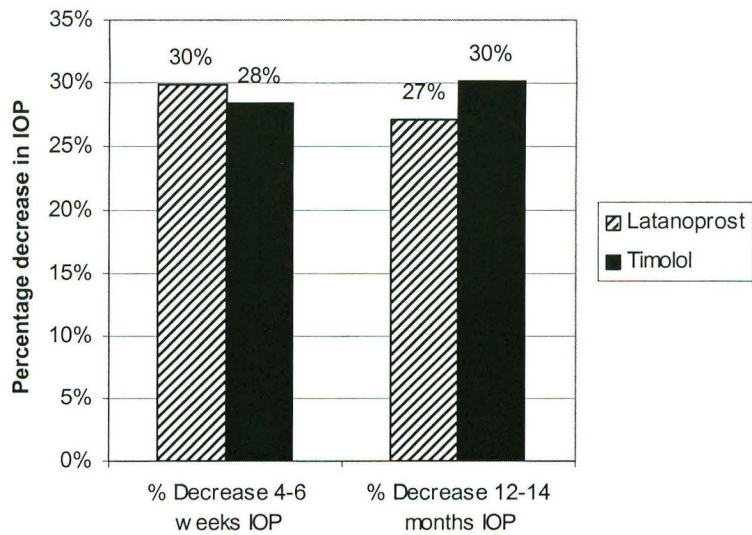


Figure 5. A bar graph depicting the decrease in IOP in eyes treated with latanoprost vs. those treated with timolol, as described in Table 1

DISCUSSION

Treatment for POAG generally involves the initiation of topical medications that work to either decrease the production of aqueous humor, or increase its outflow either through the trabecular meshwork or uveoscleral outflow. Topical beta-blockers function by decreasing aqueous production and prostaglandin analogs increase uveoscleral outflow. Other studies have noted a mean reduction in IOP of 20-40% with timolol and 20-30% with latanoprost.⁴ We noted a greater reduction in IOP with latanoprost, as compared with timolol. In our study the mean reduction in IOP was measured at 27% with latanoprost and 30% with timolol. A greater reduction was reported in a study done by Sihota et al who measured an IOP lowering effect of

greater than 30% from baseline for timolol and 43% for latanoprost. Sihota et al also evaluated circadian rhythm in patients with chronic primary angle closure glaucoma before and after therapy.⁷ Their study noted a greater reduction in peak and trough IOP measurements with latanoprost compared to timolol. Though timolol was equally effective in all circadian rhythm IOP measurements, latanoprost was less effective in peaks occurring in the evening. This can be explained, in part, by the dosing regimen of each drug, timolol (morning and evening) and latanoprost (at bedtime).

Boger was one of the first to introduce the term “long-term drift” to describe the reported diminishing IOP reduction during treatment with topical ocular hypotensive therapy. In this study, long-term drift was defined as an increase in IOP of 5mmHg or more as compared with the first post-treatment measurement.⁶ Several controlled studies have found conflicting results in whether or not long-term drift actually occurs with either timolol or latanoprost. In our study, we determined that 0% of eyes treated with timolol demonstrated this effect, as compared with 12.9% of eyes treated with latanoprost. Therefore, our results indicate that only a small percentage of POAG patients developed a tolerance to either latanoprost or timolol.

It is important to schedule the follow-up exams of glaucoma patients around the time that the highest IOP is expected. Since our study was retrospective, we were unable to account for diurnal variation in our mean IOP readings. Therefore, we were unable to predict, with certainty, the actual pressure lowering effects of these drugs. In addition, some of the subjects used in this study were also undergoing treatment with systemic beta-blockers, which are also known to cause an additional reduction in IOP.

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