

# Comparison of the Effect of Topical 0.5% Timolol Maleate and 4% Pilocarpine on the Ocular Tear Film pH of Patients with Primary Open Angle Glaucoma

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## ABSTRACT

The pH is a logarithmic scale used to specify the acidity or basicity of an aqueous solution. This study was carried out to compare the effect of 0.5% timolol maleate and 4% pilocarpine eye drops on the ocular tear film pH of subjects with primary open angle glaucoma. The study was a clinical study carried out at the Optometry Teaching Clinic, Federal University of Technology, Owerri, Nigeria. The subjects were divided into two groups of 84 subjects each. The ocular tear film pH was measured using sterile pH strips. The base line tear film pH was taken first. The first group was administered with one drop of 0.5% timolol maleate eye drop and the ocular tear film pH was measured again after 4 hours and after 24 hours. The second group was administered with one drop 4% pilocarpine eye drop and the ocular tear film pH was measured after 4 hours and after 24 hours. Results showed the mean pH values before administration with timolol eye drop was  $6.94 \pm 0.48$  in group one and  $6.98 \pm 0.51$  before administration of pilocarpine in group two. After 4 hours, the mean pH was  $7.02 \pm 0.29$  among subjects administered with timolol and  $6.14 \pm 0.57$  among subjects administered with pilocarpine. After 24 hours, the mean pH was  $6.97 \pm 0.46$  among subjects administered with timolol and  $6.95 \pm 0.48$  among subjects administered with pilocarpine. SPSS statistical analysis using the Paired Sample T test at 0.05 level of significance showed there was a significant difference ( $P < 0.05$ ) in ocular tear film pH after 4 hours of administration among subjects administered with 0.5% timolol maleate eye drop and subjects administered with 4% pilocarpine eye drop. After 24 hours of administration, there was no significant difference ( $P > 0.05$ ) in the ocular tear film pH. Timolol eye drop (0.5%) was found to be safer with regards to changes in the ocular tear film pH.

**Key words:** Timolol maleate, Pilocarpine, pH, Tear film, Glaucoma

## INTRODUCTION

Primary Open Angle Glaucoma is a chronic disease of the eye which is a major cause of blindness all over the world. Management of glaucoma is a multi-prolonged approach which involves simple observation and investigation to medical treatment, laser therapy and various types of surgery. [1] Most treatments for glaucoma are designed to lower and/or control intraocular pressure (IOP), which can damage the optic nerve that transmits visual

information to the brain. Glaucoma eye drops often are the first choice over glaucoma surgery and can be very effective at controlling IOP. [2] Elevated intraocular pressure (IOP) is accepted as the single most important risk factor for primary open angle glaucoma. Topical anti-glaucoma eye drops are used to control the intraocular pressure of the eye. [3] Following topical instillation, the drug mixes with the tears in the cul-de-sac. Bulk of the drug is lost through the lacrimal drainage system

while small amount mixes with the pre-corneal tear film and enters the cornea. The extent of pre-corneal film saturation governs the amount of drug crossing the cornea and the bioavailability of the drug.<sup>[3]</sup>

Pilocarpine is a miotic drug that relieves the pupillary block and also pulls the iris away from the anterior chamber angle. It increases the trabecular outflow due to ciliary body contraction. This results in a pull on the scleral spur and strengthening of the trabecular clamps.<sup>[4]</sup> It is available in various concentrations ranging from 0.5 - 4% and is indicated in acute and chronic narrow angle glaucoma, open angle glaucoma and in secondary glaucoma resulting from pupillary block. Its onset of action is rapid, peak effect occurs between 30-60 minutes and lasts for 4-8 hours.<sup>[4]</sup> Occasionally drug resistance can develop which is reversible. Ocular side effects are common with pilocarpine and can interfere with the patient's quality of life and compliance with recommended therapy. Timolol maleate was the first topical beta adrenergic antagonist approved in US for the treatment of glaucoma and elevated IOP.<sup>[5]</sup> It is currently the proto type agent to which new anti-glaucoma drugs are compared in clinical trials. Timolol inhibits both beta 1 and beta 2 adrenergic activity. It is being used extensively worldwide as a first line agent for the treatment of patients with open angle glaucoma and ocular hypertension. It is instilled as one drop of 0.25% or 0.5% solution twice a day and the duration of action exceeds 7 hours.<sup>[6]</sup> At this dose timolol produces a significant reduction in IOP in most cases. Although numerous investigators have demonstrated the safety of timolol, significant local and systemic side effects has been documented, so this drug must be used with caution. Although several studies<sup>[5,7]</sup> have confirmed the continued efficacy of chronic timolol therapy in a significant number of cases, the pressure responsiveness decreases with continuous use.

The tear film is the fluid covering the cornea and conjunctiva. It is also called

the pre-corneal film.<sup>[8]</sup> The tear film is responsible for providing a smooth refractive surface for clear vision, maintaining the health of the corneal and conjunctival epithelia and acting as the first line of defense against microbial infections. The pH is a logarithmic scale used to specify the acidity or basicity of an aqueous solution.<sup>[9]</sup> Solutions with a pH less than 7 are acidic and solutions with a pH greater than 7 are basic. The pH of the tear fluid is one of its physical and chemical properties that contribute to the health and function of the anterior ocular tissues. Although fluctuations in the normal pH of the pre-ocular tear fluid have been noted,<sup>[10]</sup> this fluid usually maintains a relatively stable pH environment for the anterior ocular tissues. The tear pH has a broad spectrum of values and range between 5.2 and 8.6 with an average of 7.45.<sup>[11]</sup> The tear pH tends to shift towards the alkaline side as the day progresses but is more acidic following prolonged eye closure as seen during sleep.

Eye drops are saline-containing drops that rely on absorption through the epithelium of the conjunctival sac to produce their effects.<sup>[12]</sup> Eye drops commonly used in clinics do have varying pH values. The use of such drops in the initial management of eye problems may influence the accuracy of pH measurement of the eye, and subsequently influence its management. The objective of this study is to compare the effect of 0.5% timolol maleate and 4% pilocarpine eye drops on the ocular tear film pH of subjects with primary open angle glaucoma.

## MATERIALS AND METHODS

This study was a clinical study carried out at the Optometry Teaching Clinic, Federal University of Technology, Owerri, Nigeria. Patients who were diagnosed of primary open angle were used for this study. Ethical approval for this study was obtained from the ethical committee of School of Health Technology, Federal University of Technology, Owerri, Nigeria. An informed consent was also obtained

from the subjects who participated in the study. The subjects were divided into two groups. The ocular tear film pH was measured using sterile pH strips. The base line tear film pH was taken first. The first group was administered with one drop of 0.5% timolol maleate eye drop and the ocular tear film pH was measured again after 4 hours and after 24 hours. The second group was administered with one drop 4% pilocarpine eye drop and the ocular tear film pH was measured after 4 hours and after 24 hours.

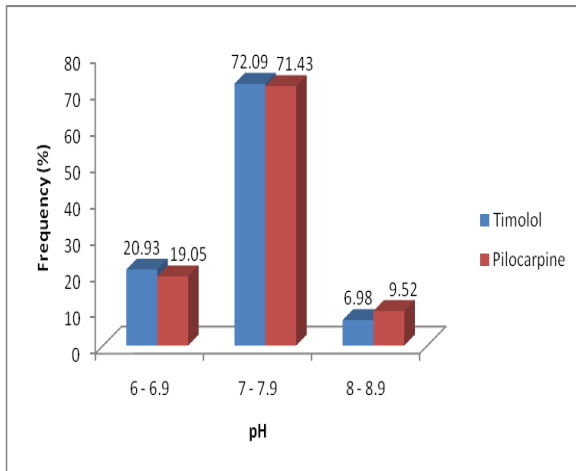
## RESULTS

A total of 168 glaucoma subjects were used for this study. Each group comprised 84 subjects. The first groups were administered with 0.5% timolol eye drop while the second groups were administered with 4% pilocarpine eye drop. The pH value of timolol maleate was 7 while the pH of pilocarpine was 4.5 (Table 1). Figure 1 showed that before administration of timolol and pilocarpine eye drops, subjects with a pH of 6 to 6.9 were 20.93% of the group administered with timolol and 19.05% of the subjects administered with pilocarpine. Subjects with a pH of 7 to 7.9 were 72.09% of the group administered with timolol and 71.43% of the subjects administered with pilocarpine. Subjects with a pH of 8 to 8.9 were 6.98% of the group administered with timolol and 9.52% of the subjects administered with pilocarpine. Figure 2 showed that 4 hours after administration of timolol and pilocarpine eye drops, subjects with a pH of 5 to 5.9 were 0% of the group administered with timolol and 26.19% of the subjects administered with pilocarpine. Subjects with a pH of 6 to 6.9 were 6.98% of the group administered with timolol and 57.14% of the subjects administered with pilocarpine. Subjects with a pH of 7 to 7.9 were 90.70% of the group administered with timolol and 16.67% of the subjects administered with pilocarpine. Subjects with a pH of 8 to 8.9 were 2.32% of the group administered with timolol and 0% of the subjects administered

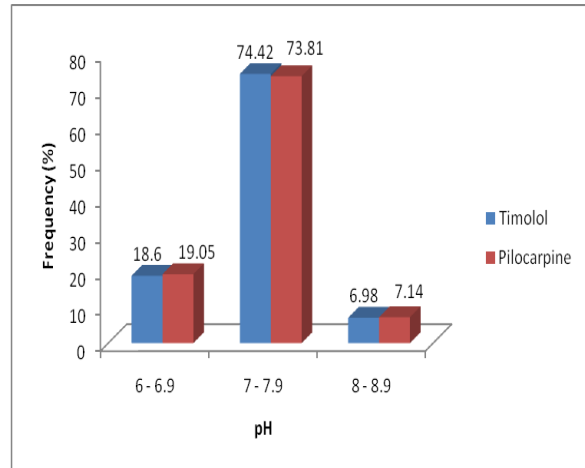
with pilocarpine. Figure 3 showed that 24 hours after administration of timolol and pilocarpine eye drops, subjects with a pH of 6 to 6.9 were 18.60% of the group administered with timolol and 19.05% of the subjects administered with pilocarpine. Subjects with a pH of 7 to 7.9 were 74.42% of the group administered with timolol and 73.81% of the subjects administered with pilocarpine. Subjects with a pH of 8 to 8.9 were 6.98% of the group administered with timolol and 7.14% of the subjects administered with pilocarpine. Table 2 showed that before administration of timolol eye drop in the first group, the mean pH value was 6.94. After 4 hours, it became 7.02 and after 24 hours, 6.97. Among the second group administered with pilocarpine eye drop, the mean pH value was 6.98 before administration; 6.14 after 4 hours and 6.95 after 24 hours (Table 3). Figure 4 showed the comparison of the mean tear film pH values. The mean pH values before administration with timolol eye drop was 6.94 in group one and 6.98 before administration of pilocarpine in group two. After 4 hours, the mean pH was 7.02 among subjects administered with timolol and 6.14 among subjects administered with pilocarpine. After 24 hours, the mean pH was 6.97 among subjects administered with timolol and 6.95 among subjects administered with pilocarpine. Statistical analysis with the Statistical Package for Social Sciences (SPSS) version 21 using the Paired Sample T test to compare the ocular tear film pH values of the subjects administered with timolol and the subjects administered with pilocarpine at 0.05 level of significance showed a P value of 0.28 before administration, 0.00 after 4 hours and 0.79 after 24 hours (Table 4). Hence, while there was no significant difference ( $P > 0.05$ ) in ocular tear film pH among the 2 groups before and after 24 hours of administration, there was a significant difference ( $P < 0.05$ ) in ocular tear film pH after 4 hours of administration.

**Table 1: pH of anti-glaucoma drugs used for the study**

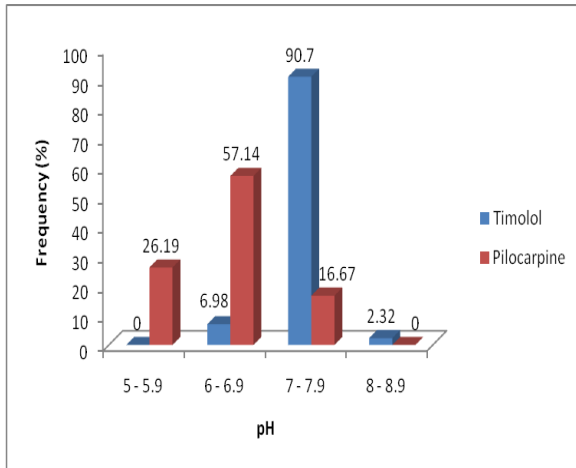
Anti-glaucoma drug	pH
Timolol (0.5%)	7
Pilocarpine (4%)	4.5



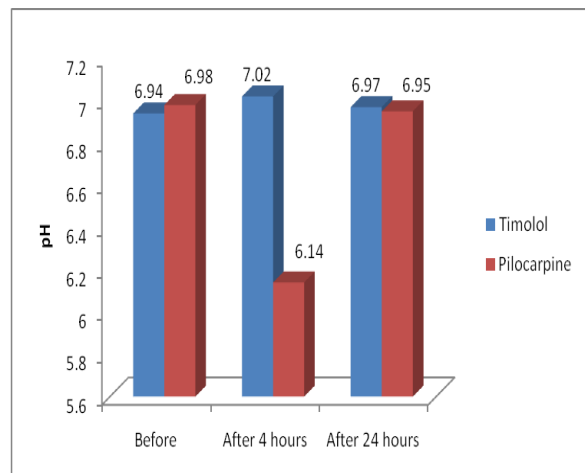
**Figure 1: Distribution of ocular tear film pH before administration 0.5% Timolol maleate and 4% Pilocarpine**



**Figure 3: Distribution of ocular tear film pH 24 hours after administration 0.5% Timolol maleate and 4% Pilocarpine**



**Figure 2: Distribution of ocular tear film pH 4 hours after administration 0.5% Timolol maleate and 4% Pilocarpine**



**Figure 4: Comparison of mean ocular tear film pH values before and after administration of 0.5% Timolol maleate and 4% Pilocarpine**

**Table 2: Descriptive Statistics of ocular tear film pH values with administration of 0.5% Timolol**

Time	n	Min. value	Max. value	Mean	Std. Dev.
Before	84	6	8	6.94	0.48
After 4 hours	84	6	8	7.02	0.29
After 24 hours	84	6	8	6.97	0.46

\*n = Number; Min = Minimum; Max = Maximum; Std. Dev. = Standard Deviation

**Table 3: Descriptive Statistics of ocular tear film pH values with administration of 4% Pilocarpine**

Time	n	Min. value	Max. value	Mean	Std. Dev.
Before	84	6	8	6.98	0.51
After 4 hours	84	5	7	6.14	0.57
After 24 hours	84	6	8	6.95	0.48

\*n = Number; Min = Minimum; Max = Maximum; Std. Dev. = Standard Deviation

**Table 4: P values for statistical comparison of ocular tear film pH values of subjects administered with 0.5% Timolol maleate and 4% Pilocarpine**

Time	P value
Before	0.28
After 4 hours	0.00
After 24 hours	0.79

## DISCUSSION

An elevated intraocular pressure remains the known cause of optic nerve damage which occurs in primary open angle glaucoma.<sup>[13]</sup> This means that by constantly keeping the intraocular pressure within

normal levels, the glaucoma patient is expected to live a healthy life. The glaucoma patient will have to apply anti-glaucoma eye drops on the long term to ensure that his intraocular pressure is maintained within normal levels. Anti-glaucoma drugs aim at controlling the intraocular pressure of the eye and this is the goal of eye care professionals when managing the disease. Timolol eye drop is one of the most commonly prescribed anti-glaucoma drugs and it is widely used among eye care practitioners in Nigeria. With a pH of 7, the timolol eye drop used in this study did not have any significant change on the ocular tear film pH. Studies [14] however, have found long-term instillation of timolol to impair the tear film stability. Kuppens, et al. [15] reported that the use of timolol eye drop resulted in lower tear break up time values among patients with primary open angle glaucoma when compared with healthy subjects. In another study [16] on patients with primary open angle glaucoma, it was found that treatment with topical 0.5% timolol eye drop lead to transient reduction in tear production.

Pilocarpine is a direct-acting cholinergic drug that reduces IOP by enhancing aqueous outflow. [17] Prolonged usage of the drug can result in permanent miosis. The mean ocular tear film pH reduced from 6.98 to 6.14 after 4 hours. It then increased back to 6.95 after 24 hours. With a pH value of 4.5, the pilocarpine eye drop used in this study had a significant reduction on the ocular tear film pH within its peak concentration period of 4 hours. The reduction in pH values after the peak period of 4 hours was found to be statistically different ( $P < 0.05$ ) with the pH values after 4 hours of administration with timolol when analyzed using the Paired sample T test (table 4). Longwell, et al. [18] reported changes in tear film pH within 1 hour of pilocarpine instillation. Ahmed and Patton [19] reported a reduced pH value with the use of pilocarpine eye drops. Pilocarpine has been reported to have localized side effects such as brow aches, accommodative

spasms and reduced vision secondary to miosis. [20]

## CONCLUSION

In conclusion, while 0.5% timolol maleate eye drop did not have any significant change in the ocular tear film pH, pilocarpine eye drop significantly reduced the tear film pH when instilled into the eye within 4 hours. However, the pH gradually returns to its normal level within 24 hours. Pilocarpine therefore should not be used for long term treatment of glaucoma. In addition to causing miosis, it can disrupt the normal pH levels and shift it toward increased acidity. Timolol is relatively safer with regards to the ocular tear film pH.

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