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Acute Effect of Timolol (Ivytimol) on Tear Production in Young Adults

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ABSTRACT

Background: Timolol Maleate is a widely used topical beta-blocker medication for treatment of glaucoma and ocular hypertension in Nigeria and globally. While effective in lowering intraocular pressure, it has been associated with adverse ocular surface effects. This study aimed to investigate the acute effect of Timolol (Ivytimol) on tear production in young adults, examining potential gender and age-related influences.

Methods: A prospective, quasi-experimental (pre-test, post-test) study was conducted on 132 healthy subjects (64 males, 68 females) aged 16-30 years (mean age 21.56 ± 2.38 years) at the University of Ilorin Optometry Clinic. Tear production was measured using Schirmer's test I without anesthesia at baseline and at 30, 60, and 90 minutes after instillation of Ivytimol (Timolol maleate BP 0.5%, Benzalkonium Chloride BP 0.01%). Subjects with ocular or systemic diseases, contact lens wearers, and those using medications affecting intraocular pressure or tear secretion were excluded.

Results: A significant decrease in tear production was observed at all time intervals following Timolol administration ($p < 0.05$) showing timolol inhinbits the production of tears. Neither gender nor age had a significant influence on the effect of Timolol on tear production ($p > 0.05$).

Conclusion: Topical administration of Timolol significantly reduces tear production in young adults, with the effect persisting for at least 90 minutes post-instillation. These findings suggest the need for close monitoring of ocular surface health in patients using Timolol, particularly for those with pre-existing dry eye or at risk of developing ocular surface disorders.

Keywords: Dry eye, Ocular hypertension, Post-instillation, Tear production, Timolol.

1. INTRODUCTION

A stable preocular tear film is a sign of good ocular health, since it serves as the primary refracting surface for light entering the visual system while also protecting and moisturizing the cornea and generating a secure and lubricated environment for the tissues of the palpebral and bulbar surfaces [1]. The tear film is the eye's first barrier against the external environment. A tear film deficit is frequently associated with symptoms of discomfort in the eyes, and as the first refractive surface of the eye, it plays a crucial role in maintaining clear vision [2]. Long-term use of topical drugs has been shown in experimental and clinical studies to cause ocular discomfort, tear film instability, conjunctiva inflammation, subconjunctival fibrosis, epithelial apoptosis, corneal surface impairment, and an increased risk of failure for further glaucoma surgery, potentially leading to visual loss [3]. Timolol maleate has been used in glaucoma therapy for almost 40 years. Timolol was originally designed for systemic usage before being successfully adopted by ophthalmologists to treat glaucoma and ocular hypertension. Since 1977, it has been shown to be an effective and safe topical medication for long-term IOP reduction [4]. A retrospective investigation reported

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that elevated IOP was more common in chronic uveitis, particularly as age and duration of uveitis increased [5]. Uveitis and its treatment can result in high intraocular pressure (IOP). A prolonged rise in IOP can lead to glaucomatous optic neuropathy and loss of visual field [6]. All types of ocular trauma have the tendency of causing an increase in intraocular pressure (IOP) in the injured eye via a variety of processes. Without proper treatment, this might cause irreversible glaucomatous damage to the optic nerve and possibly lifelong loss of visual function [7]. Over decades, Timolol maleate has been traditionally employed in the management of intraocular pressure not only in glaucoma and ocular hypertension but also other ocular conditions such as chronic/acute uveitis and also ocular trauma which can result in secondary glaucoma if not properly managed. Timolol reduces IOP in normal and glaucomatous eyes without changing visual acuity, accommodation, or pupil size. On average, timolol lowers IOP by about 5 mmHg over a 6–12 months period [8]. Tears are essential for preserving the health of the ocular surface, and any disruption in this balance might result in ocular surface conditions including dry eye syndrome [9]. While timolol is commonly used therapeutically, few studies have investigated its impact on tear production. The literature that is now available mostly concentrates on how well timolol lowers intraocular pressure (IOP), with little attention given to how it can affect tear production and quality. It is essential to investigate if timolol's ocular side effects extend beyond IOP control.

2. MATERIALS AND METHODS

2.1 Materials

The materials and instruments used for the study were Direct ophthalmoscope (Keeler), Non-contact Tonometer, Pen light (Reister), Stop clock, 5x 35mm Whatmann no. 41 filter strips (Schirmer strips) and Timolol (0.5%).

2.2 Method

This was a prospective study carried out in University of Ilorin, Optometry clinic in which the pre-test, post-test design was employed to determine the effect of Timolol on tear production. There were 132 participants randomly selected in this study between the age of 16 to 30 years because people within this age range usually have minimal ocular or systemic pathological conditions which might give an erroneous result and consent was sought from each subject. All the subjects were free from ocular and systemic diseases. They went through a pre-study measurement of tear production using Schirmer's tear strip. The baseline tear production was taken prior to the administration of Timolol and the induced tear production was measured after stipulated time intervals (30 minutes, 60 minutes and 90 minutes) respectively.

2.2.1 Ophthalmoscopy

The direct ophthalmoscope was used to observe the interior part of the eye. The ocular media, fundal background, optic nerve head, retinal vessels and macula were inspected. The disc was observed for size, shape and normal physiological cupping. While the vessels were observed for the ratio of the diameter of veins to arteries and presence of macular reflex, exudates, pigmentation and degeneration, Subjects with pathologies were screened out.

2.2.2 Intraocular Pressure (IOP) Test

Non-Contact Tonometer was used to check the IOP of each participant to rule out any subject that was suitable for the study (IOP less than 11mmHg).

2.2.3 Schirmer's Test

This test was carried out with a 5 x 35mm strip of Whatmann #41 filter paper (Schirmer strips). The paper had a notch located 5mm from one end of the strip. The notched end of the strip was rounded. The test was done by bending the strip at the notch. The rounded end of the Schirmer's sterile paper strip was then inserted into the lower conjunctival sac of the right eye. The right eye was then closed; the strip was progressively wetted by the capillary action drawing up tears as they were produced. The amount of wetting was measured after 5mins. The amount of wetting was measured from the notch of the strip as the zero point. The test was read by removing the strip from the right eye and recording the length of the moistened area. This served as the baseline/control for the experiment. 15 - 30mm of wetting in 5mins was considered normal (Lippincott, 1999). After 5mins, when the subject was calm, a drop of Timolol (0.5%) was instilled into the right eye. The tear production reading of the right eye (OD) was recorded at 30-minute intervals, three times (30 minutes, 60 minutes and 90 minutes).

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2.3 Statistical Analysis

The results of the studies are expressed as mean ± standard error of the mean (SEM) and the data were represented in tables, figures and analyzed using t-test. The statistical value, $p < 0.05$ was set as the statistically significant difference level.

3. RESULTS

In this study, one hundred and thirty-two participants were examined, 51.5% were females and the remaining 48.5% were males. All participants were within the age range of 16- 30 years with a mean age of 21.56 ± 2.38 years (Mean ± SD) and those in the age range of 21 – 25 years, had the highest frequency (56.8%) while those in age range within 26 – 30 years had the lowest frequency as shown in table 1.

Table 1: Distribution of Participants according to their Age and Gender

Age range	Male	Female	Total
16-20yrs	21 (15.9%)	27 (20.4%)	48(36.4%)
21-25yrs	39(29.5%)	36(27.2%)	75(56.8%)
26-30yrs	4(3%)	5(3.7%)	9(6.8%)
Total	**64(100%)**	**68(100%)**	**132(100%)**

Table 2 shows a decrease in tear production from baseline tear volume at time intervals of 30, 60 and 90 minutes after the instillation of ivytimol and there is little reduction in tear volume between 60 and 90 minutes of administration. Therefore, the major reduction occurs at 30mins after administration.

Table 2: comparison of the mean baseline tear production with the mean tear production 30, 60 and 90 minutes after the instillation of Ivytimol for all participants

	Baseline	30 minutes	60 minutes	90 minutes
Mean	25.97	22.32	20.95	20.77
N	132	132	132	132
Std. Deviation	9.830	10.694	10.915	11.407

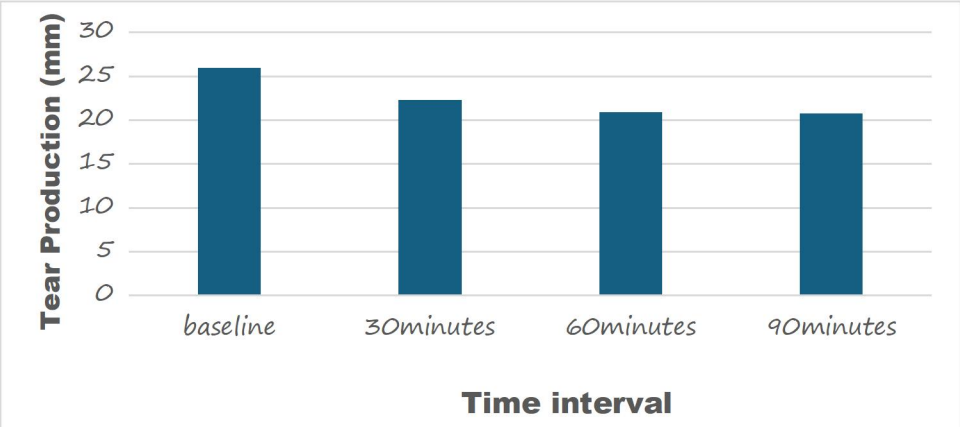

Figure 1: Mean Tear Production at different time interval

Table 3 reveals the mean decrease and percentage decrease in tear production from baseline tear production at all time intervals. After 30minutes of administration, there was 3.65 (14.05%) decrease, after 60 minutes, there was 5.02 (19.32%) decrease and after 90 minutes, there was 5.20 (20.02%) decrease in tear volume.Table 3: Percentage Mean decrease in tear production (TP) mm of subjects from Baseline at Time Intervals of 30, 60 and 90 minutes after Administration of Ivytimol

Mean Baseline Tear Production = 25.97	Mean Tear Production Values	Mean Decrease of Tear Production	Percentage Decrease %
30 minutes	22.32	3.65	14.05
60 minutes	20.95	5.02	19.32
90 minutes	20.77	5.20	20.02

Table 4 reveals the baseline for tear production and the effect of ivytimol on tear production for both male and female, there was no significant difference (P>0.05) between the mean baselines tear production in both male and female using independent t test (P= 0.737). There was a significant reduction in tear production in both gender across all the time interval with P =0.009 and 0.033 for male and female respectively.

Table 4. Effect of Ivytimol on Tear production from Baseline through Time Intervals of 30, 60 and 90 minutes after administration with respect to Gender

Sex		Baseline	30 minutes	60 minutes	90 minutes
M	Mean	25.67	22.52	20.39	20.08
	N	64	64	64	64
	Std. Deviation	9.167	10.356	10.606	11.387
F	Mean	26.25	22.13	21.47	21.41
	N	68	68	68	68
	Std. Deviation	10.476	11.078	11.251	11.473
Total	Mean	25.97	22.32	20.95	20.77
	N	132	132	132	132
	Std. Deviation	9.830	10.694	10.915	11.407

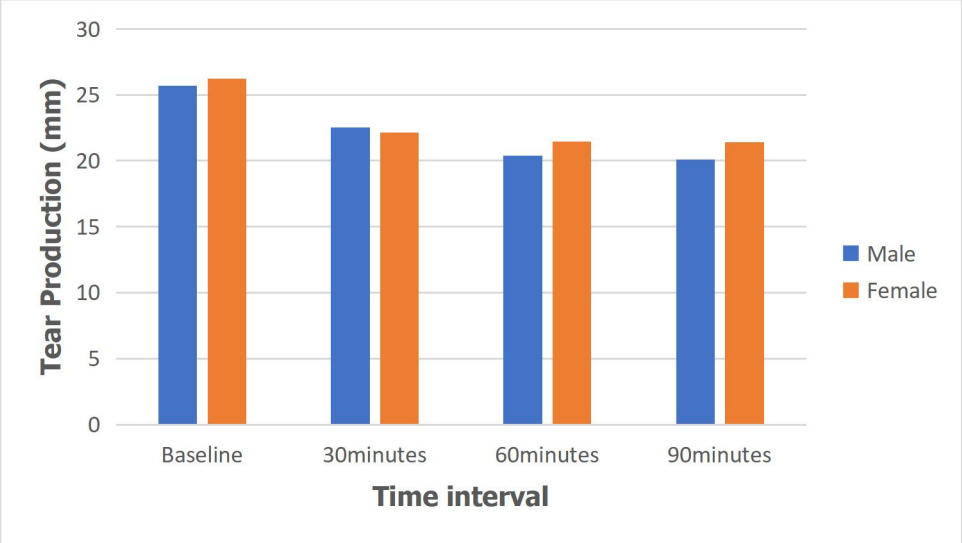

Figure 2: Tear production from Baseline through Time Intervals after the administration of Ivytimol for both male and female subjects.

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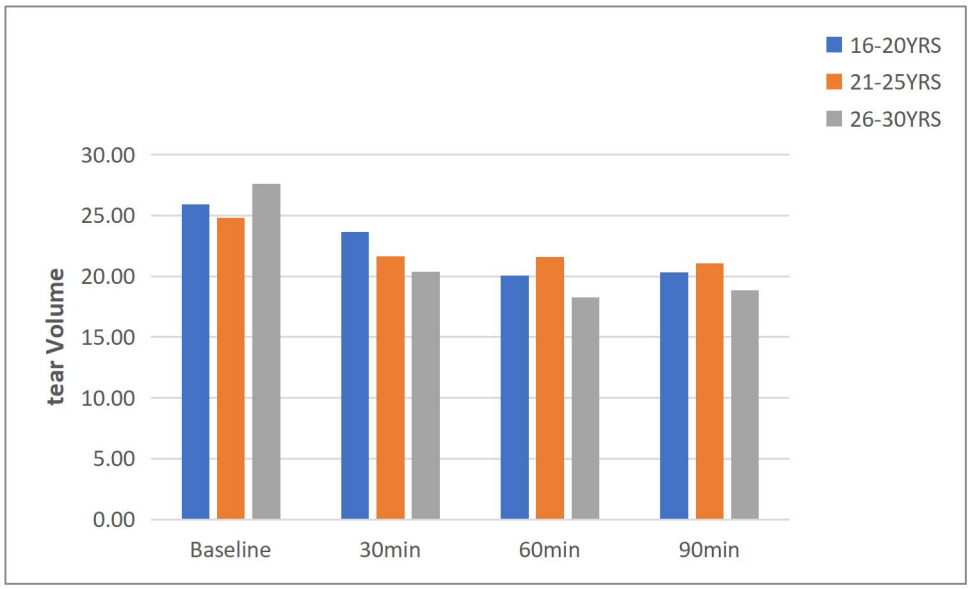

Figure 3: Tear production from Baseline through Time Intervals of 30, 60 and 90 minutes after administration of Ivytimol with respect to Age.

There was no significant difference in the tear production in both male and female subjects across all the time intervals (P=0.77). Figure 3 shows the baseline for tear production and at various time interval after the administration of ivytimol across different age group. There was no significant difference (P>0.05) in tear production across different age group at various time interval (P= 0.86).

4. DISCUSSION

Timolol, a beta-adrenergic receptor blocker with non-selective properties, is commonly prescribed as an initial treatment for glaucoma and elevated intraocular pressure in Nigeria, owing to its proven effectiveness and affordability [10]. While beta-blockers are widely used, they have been linked to various complications affecting the ocular surface, with reduced tear production being one of the noted side [11]. Despite the extensive use of Timolol across Nigeria, there is a notable lack of research examining its effects on tear production, particularly in the country's northern regions. This study aimed to address this research gap by investigating the impact of Timolol on tear production specifically in Nigeria's North Central geopolitical zone. This area is characterized by unique climatic and environmental conditions that may influence ocular surface health. One hundred and thirty-two (132) participants were examined, a total of 64 male participants and 68 female participants were used in this study, all participants were within the age range of 16- 30 years with a mean age of 21.56 ± 2.38 years. A statistical analysis employing the t-test method demonstrated that topical application of Timolol significantly affects tear production. The study observed a sequential decline in tear production following Timolol administration. From an initial measurement of 25.57 ± 9.830, tear production decreased to 22.32 ± 10.694 after 30 minutes, further reduced to 20.94 ± 10.915 at the 60-minute mark, and reached 20.77 ± 11.407 by 90 minutes post-application. These findings corroborate with a research done by Patel el al which indicated that subjects using topical beta-blockers exhibited considerably diminished tear production compared to non-users, as determined by Schirmer's test [12]. The study had a relatively balanced gender distribution, with 51.5% females and 48.5% males. This balanced representation of both genders enhances the generalizability of the findings. The mean distribution of tear production in both genders at different time intervals after the administration of Timolol revealed that there was no significant difference (P>0.05) between the mean baselines tear production in both male and female, only that there was a significant reduction in tear production in both gender across all the time interval with P =0.09 and 0.333 for male and female respectively. This result is in accordance with the study conducted by Ozdemir and Temizdemir in 2010, they found no statistically significant difference in the Schirmer test results between males and females [13]. However, the

Schirmer test values were observed to gradually decrease with advancing age in both genders. Also, another hospital-based study in Nigeria by Onwubiko et al [14] concluded that gender does not have a significant influence on the prevalence of dry eye disease. This is in contradistinction to some previous studies which indicated that gender has a significant influence on Tear Production, a study by Onua and Chukwuka [15] agreed with this, also Shanti et al [16] study revealed a significant correlation between dry eye disease (DED) and gender, with females being 1.5 times more likely to develop DED compared to males. Though from the study, there's an indication of a sex-specific difference in tear production response to Timolol, with females showing a marked decrease tear production at 30 minutes post-administration compared to males at 60 minutes. This disparity may be attributed to hormonal influences on lacrimal gland function [17]. Women generally have lower androgen levels than men, potentially contributing to reduced basal tear production [18]. This research also examined how age influences Timolol's effect on tear production, with measurements taken at baseline and at 30, 60, and 90 minutes post-administration. There was no significant difference ($P>0.05$) in tear production across different age group at various time interval ($P= 0.86$). This report was similar to a study carried out by Ibanga *et al* [19] in southern Nigeria and also a study carried out by Bukhari *et al* [20] which showed no difference in dry eye prevalence with respect to age. Some other researchers like Ding *et al* [21] and Sullivan *et al* [17] have a contrary opinion, according to their study, aging significantly affects the meibomian gland, leading to decreased lipid production and increased tear evaporation. Also research by Rico-del-Viejo *et al*. [22] showed that aging affects various ocular surface parameters, including tear film stability and volume, supporting the notion that tear production diminishes with age indicating reduced tear production and stability in older individuals. The discrepancies in the findings may be attributed to variations in the study's design, specifically differences in population demographics, sampling techniques, and methodological approaches. These divergences could include factors such as: Distinct population characteristics, like age, ethnicity, or geographic location also variations in research protocols, such as data collection tools, diagnostic criteria, and analytical techniques.

5. CONCLUSION

The results highlight the importance of monitoring patients for dry eye symptoms when initiating Timolol therapy, particularly in regions with challenging environmental conditions such as Nigeria's North Central zone. Healthcare providers should consider regular assessment of tear production and ocular surface health in patients receiving long-term Timolol treatment.

DECLARATIONS

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Declaration of interest statement

The authors declare no conflict of interest regarding this study.

Contribution of the Authors

Oluwasola M. Ojo conceptualized, designed, and analyzed the research. Haira M. Lawal contributed to data collection and manuscript preparation. Ayodeji E. Ige and Ebunoluwa A. Ajibola-Ajo participated in the review and editing of the manuscript for publication.

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