AFRICAN JOURNAL OF MEDICINE and medical sciences

Volume 37 Number 1 March 2008

ISSN 1116—4077

Afr. J. Med. Med. Sci. (2008) 37, 43-47

The effect of timolol maleate on tear film break-up time in Nigerians

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Summary

The aim of this study was to evaluate the effect of Timolol maleate on tear film break-up time in a Nigerian population. 192 eyes of 96 subjects were examined in a hospital based case-control study after being administered pre-coded questionnaires. The mean tear film break-up time was measured. There was significant difference (t=10.164,*P*<0.001) in the mean break-up time of cases(10.45secs) and controls(30.18secs).Half of the cases had some ocular discomfort with the instillation of Timolol maleate, a significant number of them having just been commenced on the medication (X^2=8.889,*P*=0.003). Long-term instillation of Timolol maleate impairs tear film stability. The ocular discomfort experienced by patients on Timolol may contribute to poor drug compliance observed in patients on chronic drug therapy. Regular screening of patients on Timolol maleate for tear film instability and dry eyes is important and drug manufacturers should explore the possibility of incorporating artificial tears in Timolol maleate preparation.

Keywords: *Goblet cell, tear film break-up time,timolol maleate*

Résumé

Le but de cette étude était d'évaluer l'effet de la Timolol maleate sur le temps de détachement des films des yeux dans la population Nigériane. 192 yeux des 96 individus étaient examinent à l'hôpital basée sur l'étude cas-contrôle après l'administration des questionnaires pre-codées. Le temps moyen de détachement était mesuré. Il y avait une différence significative (t=10.164, *P*<0.001) dans le temps moyen de détachement des cas (10.45secs) et les contrôles (30.18secs). La moitie des cas avaient certaines disconfort oculaire avec l'instillation du Timolol maleate, un nombre significative de ceux ci venant juste commencée la méditation (X^2=8.889, *P*=0.003). L'instillation à long terme du Timolol maleate cause une disparité de la stabilité du film. Le disconfort oculaire expérimentée par les patients sous le Timolol peut contribuer à la mauvaise mode d'indications observée chez les patients en thérapie chronique. Le test régulier des patients sous l'effet timolol maleate de l'instabilité du film et le dessèchement des yeux est important et les producteurs des médicaments doivent explorés les possibilités d'incorporer les larmes artificielles à la préparation du timolol maleate.

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Introduction

The pre-corneal tear film forms a stable and continuous covering over the exposed portion of the globe and consists of 3 discrete parts: the outermost thin superficial lipid layer secreted by the meibomian glands; the middle thicker aqueous layer secreted by the main and accessory lacrimal glands; and the innermost mucin layer secreted by the conjunctival goblet cells [1]. The tear film keeps the ocular surface wet, washes away foreign particles and contains bactericidal enzymes [2]. Periodic resurfacing of the tear film through the blinking action of the lids is essential to prevent a break-up of the pre-corneal tear film despite the relative stability of the anterior refractive surface of the eye.

Goblet cells are large, oval or round cells formed in the deepest layer of the conjunctiva, gradually passing towards the surface where they discharge their mucinouos content that adsorbs onto the corneal surface enabling aqueous and superficial lipid layers to spread spontaneously [2,3]. They are of such great importance that destruction of the lacrimal glands is relatively innocuous whereas xerosis of the conjunctiva and tear film instability occurs following their destruction [4].

Various studies [5,6] have shown goblet cell density to be significantly reduced in many ocular surface diseases including keratoconjunctivitis sicca, cicatricial ocular pemphigoid, superior limbic keratoconjunctivitis, radiation keratitis, Steven Johnson syndrome and atopic disease. Also significant reduction in goblet cells and prolonged tear film break-up time were noted in patients being treated with twice daily preparation of Timolol maleate [7].

The tear film break-up time (TBUT) is defined as the interval between a complete blink and the appearance of the first randomly distributed dry spot on the cornea [1] and it is a test commonly used for examination of the pre-corneal tear film. Norn [8] in his study reported that break-up time averages between 25 and 30 seconds in normal eyes with a wide fluctuation while Shappiro and Merin [9] found the mean break-up time in normal subjects to be 13.2+/- 3.9 seconds.

Timolol maleate is a non selective B-blocker commonly used as first choice medication for primary open angle glaucoma in most developing countries, although they are also useful in treatment of all types of glaucoma irrespective of the state of the angle [10].

Studies [11,12] have shown that quite a number of glaucoma patients on long term Timolol therapy are non compliant with their medications. Various ocular side effects have also been documented in literature with Timolol use notable among which are symptoms of dry eye state such as burning, smarting and stinging sensation. Others include blepharo-conjunctivitis, superficial punctuate keratopathy and reduced corneal sensitivity [13,14,15,16]. No such studies have been reported in any West African population.

Patients and method

A total of 192 eyes of 96 successive participants (48 cases and 48 controls) who met the specified criteria, matched by age and sex were examined over six months (from June to December 2003) The mean temperature at this period ranges between 21.4^{0}C-31.4^{0}C and relative humidity ranges from 65mmHg-96mmHg. Cases were recruited from the glaucoma subspecialty clinic of the University College Hospital (UCH), Ibadan, Nigeria and controls from the general out-patient ophthalmic clinic of same hospital. The inclusion criteria for cases were patients aged 40-69 years with primary open angle glaucoma (POAG) who had been on consistent instillation of only topical Timolol maleate 0.5% for a minimum period of 1 year prior to the study.

The participants in the control group who did not have glaucoma were matched with the case study group by age and sex. The exclusion criteria included subjects with pterygium or other degenerative ocular surface conditions, dry eye syndrome, keratoconjunctivitis sicca, blepharo-conjunctivitis, Vitamin A deficiency, trachoma or scarring of the conjunctiva or lids. Subjects who had undergone ocular or lids surgeries or who had been on other topical or systemic medications that could alter the tear film break-up time such as pilocarpine, antihistamines and atropine topically; and phenothiazines, diazepam, antihistamine and artane orally for at least 6 months before the study were excluded. Subjects who had been on any other topical eye medications within 6 weeks of the study were also excluded.

All subjects were administered with pre-coded questionnaire which included sociodemographic, drug history and family history. The best available visual acuity was assessed and pen touch and slit lamp examinations were carried out to ensure strict compliance with the specified criteria.

Those who met the inclusion criteria had their TBUT measured by only one of the investigators who did not know which participants were cases or controls, between 14.00Hrs and 17.00Hrs GMT. A fluorescein strip was moistened with one drop of sterile water and applied to the unanesthesized inferior temporal bulbar conjunctiva of the participants. They were then asked to blink several times so as to distribute the fluorescein well over the ocular surface. They were subsequently positioned for slit lamp examination, asked to stare directly ahead without blinking or holding the lids. The tear film was scanned through with a cobalt blue filtered light at a magnification of X16 and a 3mm wide vertical beam. A stop watch was used to time the interval between the last complete blink and the first appearance of a randomly distributed dry spot which appeared as black spot or streak on a yellow-green background, that is, the tear film break-up time. Three measurements were taken and an average calculated. Values greater than 15 seconds were taken as normal, less than 15 seconds were considered abnormal and values less than 10 seconds were suggestive of unstable tear film, as categorised by Lemp [1].

Data collected were entered into SPSS V.10. The mean TBUT values were compared through the use of student t-test between the two groups and associations between qualitative variables were explored by means of chi-square test. Statistical significance was determined at the 5% level of significance. Ethical approval was given by the hospital's ethical committee for the study.

Results

A total of 192 eyes of 96 subjects were studied comprising 48 cases and 48 controls. 50% of the cases had no ocular complaints, met the specified criteria were aged between 40 and 69 years and had their

break-up time measured. 50% of the cases had no ocular complaints with the drug use. 45.8% complained of peppery sensation, 2.1% complained each of burning and foreign body sensations.

Table 1: Mean break up time among cases and controls

	Mean (secs.)	Std dev.	t-value	P-value
Right Eye				
Case	10.71	5.35	9.855	P<0.001
Control	30.60	12.92		
Left Eye				
Case	10.19	4.94	9.860	P<0.001
Control	29.76	12.83		
Both Eyes				
Case	10.45	4.76	10.164	P<0.001
Control	30.18	12.57		

Table 1 shows that the mean break-up time in eyes treated with Timolol were significantly lower in the right and left eyes compared with eyes not treated with Timolol (t=10.164, $P<0.001$). A correlation coefficient between the break-up time and age in both cases and controls shows an inverse relationship. The break-up time decreased with increasing age (figures 1a and 1b). Correlation of TBUT and number of years of consistent use of Timolol showed an inverse relationship.

A higher proportion of cases (81.3%) had abnormal TBUT (<15 seconds) compared with the control group (18.7%), (X^2=37.500, $P<0.001$); while 26(54.2%) of cases had unstable tear film (TBUT < 10secs.) compared with only 4(8.3%) of controls. This was found to be statistically significant (X^2=24.264, $P<0.001$).

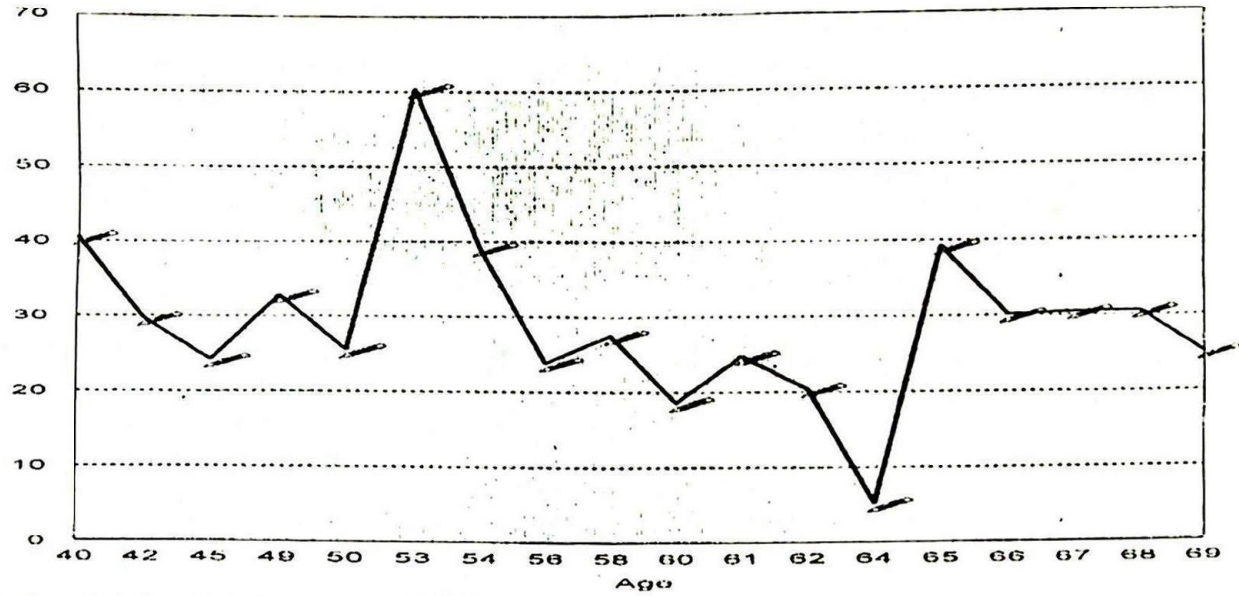

Fig. 1a: Relationship between age and TBUT among controls

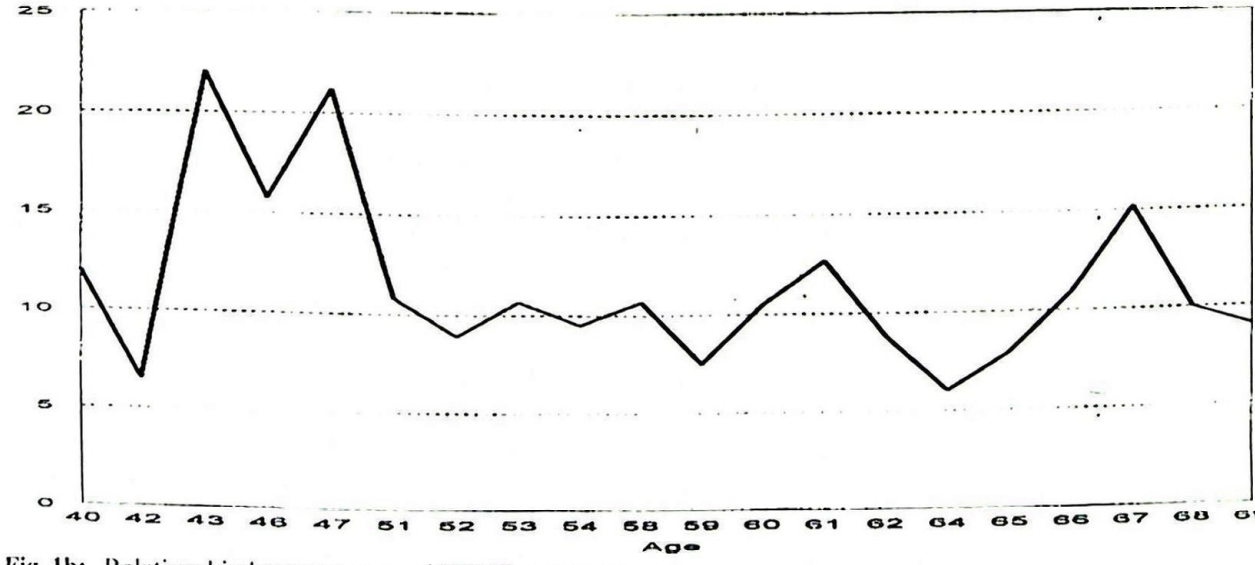

Fig. 1b: Relationship between age and TBUT among cases

Discussion

The possible effect of long term instillation of Timolol maleate on pre-corneal tear film morphology has been investigated indirectly by measuring the tear film break-up time. This is important as there have been some controversies about the effect of topical Timolol on TBUT. While Nielsen and Eriksen [17] demonstrated that Timolol did not affect the TBUT, others [7,18,19] have reported a significant reduction in TBUT in patients on long term use of Timolol.

The mean tear film break-up time was found to be significantly lower in cases (10.45seconds, SD=4.76) than in controls (30.18 seconds, SD=12.57); (t=10.164, p<0.001). Abnormal TBUT (<15 seconds) was found in 81.3% of the cases compared to only 18.7% in the controls. This was statistically significant (X^2=37.500, p<0.001). The study also showed an association between tear film instability (TBUT<10 seconds) and long term use of Timolol as 54.2% of the cases had an unstable tear film compared to 8.5% of the controls (X^2=24.264, p<0.001).

Kuppens *et al* [18] and Herreras *et al* [7] reported findings similar to these. However Nielsen and Eriksen [17] found that there was no significant influence on the tear film break-up time with Timolol treatment. However their methodology was slightly different as their measurement was taken after 4 weeks of Timolol instillation and this short period could explain the disparity observed in their result.

Medical treatment is often an effective way of controlling glaucoma [20]. However, for treatment to be effective, the side effects of drugs need to be minimal to promote good drug compliance and allow continuation of therapy. Half of the cases on Timolol in this study had ocular discomfort with the drug but claimed good compliance with the drug instillation. This good compliance was however difficult to justify as patients have been known to underestimate their level of defaulting when directly questioned [12,21]

The TBUT is a simple and objective qualitative test readily interpretable that directly measures the goblet cell function. Schirmer's test, also a popular qualitative test for assessing the pre-corneal tear film showed low correlation with TBUT in the study by Shappiro and Merin [9], who concluded that it was due to the fact that the 2 tests examine 2 different aspects of the tear film physiology. Schirmer's test assesses the adequacy of aqueous component produced by the lacrimal glands and TBUT assesses the secretion of mucin produced by the goblet cells and the meibomian glands function. The marginal tear strip, also a quantitative test of adequacy of tear film is however less sensitive.

Some controversies exist as regards whether the reduction in conjunctival goblet cell density and resultant reduction in tear film break-up time is the direct effect of Timolol maleate or due to the commonly used preservative Benzalkonium chloride in the preparation. While Kuppens *et al* [18] in their study of patients on Timolol with Benzalkonium chloride who later change to Timolol without preservative found no significant change in their TBUT, Shimazaki *et al* [19] studying changes induced in ocular surface epithelium and the tear film by antiglaucoma eye drops – Timolol with 0.005% Benzalkonium chloride and Unoprostone with 0.01% Benzalkonium chloride found TBUT to be lower in the group on Timolol. This significantly lower TBUT observed in patients on Timolol with lower concentration of Benzalkonium chloride (0.005% compared to 0.01% in Unoprostone) suggests that Timolol plays some direct role in reducing the TBUT. Ishibashi *et al* [22] however in their study found that exposure to preserved Timolol resulted in significant instability of the precorneal tear film.

This study showed that 50% of the cases complained of ocular discomfort (peppery, burning and foreign body sensations) with Timolol instillation. Similar results were also reported by Rotchford and Murphy [12] where 45% of their patients had complaints.

A correlation coefficient between mean TBUT and age in this study showed an inverse relationship as the break-up time decreases with increasing age. This was also reported by Balogun [23] and Patel *et al* [24]. There was also strong association between the TBUT of right and left eyes in both cases and controls. This supports the findings of Lemp *et al* [1] who found no statistically significant difference in right and left eyes of subjects assessed.

Conclusion

This study demonstrates an association between prolonged use of Timolol maleate eye drop and abnormal tear film break-up time. There is progressive reduction in TBUT with increasing age in cases and controls as demonstrated by previous studies and many patients on prolonged Timolol use complained of peppery ocular discomfort.

It may thus be desirable to screen patients for dry eyes before commencement and during the long term use of Timolol and encourage use of astringents like artificial tears in such patients. But this will increase the cost of treatment and promote poor compliance to therapy. Hence it is suggested that drug manufacturers explore possibility of Timolol

maleate preparation incorporating such astringents to counter the problem.

This may reduce the patients' ocular complaints leading to improved quality of life, greater compliance to medication and ultimately a better control of glaucoma in our patients.

References

1. Lemp, MA. and Hamill.Jr. J.R. Factors affecting tear film break-up in normal eyes. Arch Ophthalmol.1973; 89: 103-105.
2. Lemp M.A Pre-corneal tear film: Factors in spreading and maintaining a continuous tear film over the corneal surface Arch. Ophthal mol.1970; 83:89-94.
3. Holly F.J and Lemp M.A: Wettability and wetting of the corneal epithelium.Exp.Eye Res. 1971; 11:239-251.
4. Warwick R. Ocular Appendages. Eugene Wolfe Anatomy of the eye and the orbit. 7th Ed London, H.K Lewis & Co Ltd. 1976; 207-209.
5. Ralph R.A: Conjunctival goblet cell density in normal subjects and in dry eye syndromes. Invest Ophthalmol Vis Sci 1975; 14:299-302.
6. Kinoshita S, Kiorpes T.C, Friend J A and Thoft R.A: Goblet cell density in ocular surface disease. A better indicator than mucin Arch. Ophthalmol 1983; 101: 1284-1287.
7. Herrera's J.M, Pastor C, Calonge M and Asensio V.M: Ocular surface alteration after long-term treatment with an antiglaucoma drug . Ophthalmology 1992; 99 (7) 1082-1088.
8. Norn M.S: Desiccation of the pre-corneal film I. Corneal wetting time. Acta Opthalmologica 1969; 47: 865 – 880.
9. Shapiro A, and Merin S: Schirmer test and break-up time of tear film in normal subjects. Am J Ophthalmol, 1979; 88: 752-757.
10. Kanski J.J. The Glaucomas.Clinical Ophthalmology: A Systematic Approach 4th Ed. London, Reed Educational and Professional publishing Ltd. 1999;243-244.
11. Bloch S, Rosenthal A.R., Friedman L. and Caldarolla P. Patient compliance in glaucoma. Br. J. Ophthalmol, 1997; 61:531-534.
12. Rotchford A and Murphy K..Compliance with Timolol treatment in glaucoma. Eye 1998; 12: 234 – 236.
13. Van Buskirk E.M. Adverse reactions from Timolol administration. Ophthalmology 1980; 87:447-450.
14. Berry D.P, Van Buskirk E.M, Shields B: Betaxol and Timolol. A comparison of efficacy and side effects. Arch Ophthalmol 1984; 102: 42-45.
15. The Levobunolol study group: Levobunolol: A four-year study of efficacy and safety in glaucoma patients. Ophthalmology 1989; 96 (5): 642-645.
16. Nielsen N.V and Eriksen J.S: Timolol Transitory manifestations of dry eyes in long-term treatment. Acta Ophthalmologica 1979; 57: 418-424.
17. Nielsen N.V and Eriksen J.S. Timolol and Metoprolol in glaucoma. A comparison of the ocular hypotensive effect, local and systemic tolerance Acta Ophthalmologica 1981; 59:336-346
18. Kuppens E.V, Jong C.A, Stolwijk T.R, Keizer R.J and Van Best J.A. Effect of Timolol with and without preservative on the basal tear turn over in glaucoma. Br. J. Ophthalmol 1975; 59: 667-669.
19. Shimazaki J, Hanada K, Yagi Y. *et al*. Changes in ocular surface caused by antiglaucomatous eye drops: prospective, randomized study for the comparisons of 0.5% Timolol vs 0.12% Unoprostone. Br. J. Ophthalmol 2000; 84: 1250-1254.
20. Pisella P.J, Pouliquen P. and Baudouin C. Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. Br. J. Ophthalmol 2002; 86: 418-423.
21. Kass M.A, Meltzer D.W, Gordon M, Cooper D and Goldberg J. Compliance with tropical Pilocarpine treatment. Am J Ophthalmol 1986; 15; 10(5): 515 – 523.
22. Ishibashi T, Yokoi N and Kinoshita S. Comparison of the short term effects on the human corneal surface of topical Timolol maleate with and without Benzalkonium chloride. J. Glaucoma. 2003; 12 (6): 486-490.
23. Balogun M.M, Ashaye A.O, Ajayi B.G.K and Osuntokun O.O. Tear break-up time in eyes with pterygia and pingueculae in Ibadan. West Afr. J. of Medicine 2005; 24 (2): 162-166.
24. Patel S and Farrell J.C. Age-related changes in pre corneal tear film stability. Optom Vis Sci 1989; 66 (3): 175-178.

Received: 15/06/07
Accepted: 20/02/08