ISSN : 0300-1652

Indexed and archived with PubMed/MEDLINE

nmj

NIGERIAN MEDICAL JOURNAL

Vol. 57, Number 2, March - April 2016

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ORIGINAL ARTICLE

Effect of preserved and preservative-free timolol eye drops on tear film stability in healthy Africans

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ABSTRACT

Background: Preserved versus nonpreserved formulations for ophthalmic use have been well described in the literature although not specifically in the African population where beta blockers are frequently used as the first-line therapy due to economic and availability issues. This study sought to determine the effect of preserved and preservative-free Timolol eye drops on tear film stability in healthy black Africans. **Materials and Methods:** Sixty healthy nondry eye subjects aged 19–25 years were randomly assigned into four groups ($n = 15$) and differently treated with eye drops of phosphate buffered saline (PBS), preservative-free timolol (PFT), benzalkonium chloride (BAK) only, and BAK-preserved timolol (BPT). Noninvasive tear break-up time (NITBUT) was measured using the keratometer at baseline and 30, 60, and 90 min after drop application. **Results:** No significant decline in NITBUT was observed following treatment with PFT and PBS. However, BAK treatment showed a positive time-dependent significant decline in NITBUT ($P < 0.001$) while a significant decline in the BPT-treated group was only found at 90 min (–3.52 s; $P < 0.001$). In comparison to the PFT-treated group, treatment with BAK and BPT showed significantly lower NITBUT ($P < 0.001$). **Conclusion:** BPT is associated with a significant decline in tear film stability in black Africans. This finding has implications in the management of glaucoma in patients with high-risk of dry eyes in this population.

Key words: Benzalkonium chloride preserved timolol, glaucoma, keratometer, preservative-free timolol

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INTRODUCTION

Primary open angle glaucoma (POAG) is a group of ocular disorders characterized by high intraocular pressure, optic nerve damage, and visual field loss with an associated open anterior chamber angle. POAG is the leading cause of irreversible blindness worldwide, accounting for 8% of all blindness.[1] Sub-Saharan Africa is notably the most affected, having a crude prevalence of 4.2%,[2] and Ghana is documented to have the highest glaucoma prevalence in this sub-region.[3,4]

In general, prostaglandin analogs are now regarded as the first line of glaucoma medical therapy although beta blockers are frequently used in most African countries due to economic and availability issues. Timolol maleate, a β-blocker, is widely used either as monotherapy or in combination with other agents for the management of various types of glaucoma including ocular hypertension.[5] In Africa, it is the first line therapy for treatment of glaucoma,[6] and till date remains the gold standard for the comparison of the efficacy of other potent antiglaucoma agents.[7] Its mechanism of action is targeted toward lowering intraocular pressure by reducing the rate of aqueous production by the ciliary epithelial tissue.[8,9] Timolol is one of the cheapest ocular hypotensive agents

Access this article online	
Quick Response Code:	Website: www.nigeriamedj.com
	DOI: 10.4103/0300-1652.182071

How to cite this article: Ilechie A, Abokyi S, Boateng G, Koffuor GA. Effect of preserved and preservative-free timolol eye drops on tear film stability in healthy Africans. Niger Med J 2016;57:104-9.

and is therefore highly prescribed in resource deficient settings.[10] Timolol eye drop in multi-dose containers, like most other topical ocular medications, are preserved with benzalkonium chloride (BAK) to inhibit microbial contamination and prevent biodegradation maintaining drug potency.[11,12] However, ocular surface disorders including inflammation, conjunctival, and corneal epithelial tissue damage and tear film instability have been associated with BAK.[13] Furthermore, unpreserved timolol has been observed to interfere with the tear film in some individuals.[14] Instability of tear film on the ocular surface is a sign of dry eyes and has the potential to decrease quality of life and lead to noncompliance in the use of the antiglaucoma medication.

Studies corroborating the potential adverse effect of BAK-preserved timolol (BPT) on the tear film were mainly conducted in Caucasian populations and may not provide an adequate reflection of its effect on the African population, considering that racial variations in tear production and stability have been observed.[15] In addition, the fluorescein tear breakup time which was used in most of these studies has a shortcoming of interference with actual tear film stability of subjects.[16] Hence, current data support the use of the noninvasive procedures in the assessment of tear film stability.[17] Because glaucoma has been observed to affect basal tear secretion,[18,19] we prospectively studied healthy volunteers to compare the effects on tear film stability, of BPT, preservative-free timolol (PFT) and BAK, in black African subjects by employing a routinely used ophthalmic equipment called the keratometer.

MATERIALS AND METHODS

This was a randomised, double-blind prospective study of the effect of timolol eyedrops on tear film stability in healthy Africans carried out at the University of Cape Coast Optometric Clinic, Ghana, in the first quarter of 2012, among patients aged 19-25 yreas, following an informed consent and ethical approval by the University of Cape Coast Institutional Review Board.

Ethical considerations

The study was approved by the University of Cape Coast Institutional Review Board, and informed consent was obtained from each subject before recruitment into the study. Participation was voluntary. All protocols employed in the study were in accordance with the Declaration of Helsinki involving the use of human subjects in research.

Individuals underwent a preliminary tear function screening including Schirmer I test with anesthetic and noninvasive tear breakup time (NITBUT) following outlined protocols[17,20] for the selection of participants.

Only subjects with no ocular abnormality and not on any topical treatment were included in the study.

Subjects with a Schirmer filter wet length below 10 mm in 5 min, NITBUT below 10 s and unable to withhold a blink until distortion of the keratometer image mires were excluded.

The 60 subjects were randomly assigned into four groups (n = 15; 10 males and 5 females per group). Subjects in Group I had instilled into their eyes a single drop of PBS solution; Groups II patients had instilled into their eyes a drop of preservative-free 0.25% timolol solution; Group III patients were administered into the eyes one drop of solution containing 0.25% timolol preserved with 0.01% BAK, and in Group IV patients had instilled into the eye a solution containing only 0.01% BAK.

After administration of a drop, subjects were required to close their eyelids gently and to keep them closed for 30 s.

Assessment of noninvasive tear breakup time

The subject was comfortably seated placing chin on chin rest and forehead on head rest of a Burton® 1040 Keratometer (R.H. Burton Co., Japan). The keratometer was then adjusted and focused on the eye. With the mires in focus, the subject was asked to blink once and refrain from blinking. A stopwatch was started immediately after the last complete blink. At the first appearance of any distortion of the focusing mire, the stopwatch was stopped and the time noted. If subject blinks before measurements, the test is halted, and then repeated after several blinks. The interval between the last blink and the doubling/distortion of mires was recorded in seconds as the NITBUT. Five measurements were taken for each eye as recommended by Brown and Cho,[21] and the average of three closet NITBUT values were recorded for baseline, and 30, 60, and 90 min posttreatment.

Statistical power and analysis

The main outcome variable was NITBUT values as measured by keratometer mires. Fifteen participants in each group provided 90% power to detect a 1 s mean difference in NITBUT values by treatment. Data obtained were analyzed with the GraphPad Prism 5 (GraphPad Software, Inc., San Diego, CA). Descriptive values were expressed as mean ± standard error of mean. Variables measured satisfied the criterion for both normality (D'Agostino and Pearson omnibus tests) and equal variances (Bartlett's test for equal variances). Within-group analysis was performed for each treatment group using one-way ANOVA for repeated measures followed by Dunnett's multiple comparison *post hoc* test to compare the posttreatment NITBUT values at 30, 60, and 90 min with their respective baseline values. Between-group comparisons using one-way ANOVA followed by Dunnett's multiple comparison *post hoc* test

was employed to determine differences in NITBUT between each treatment group compared to the PFT-treated group for each period. Probability $P \leq 0.05$ were considered statistically significant.

RESULTS

Sixty subjects aged 21.36 ± 1.28 years (range, 19–25 years) participated in the study. No significant differences were observed comparing the mean ages between the four treated groups ($P > 0.05$; one-way ANOVA).

Results of NITBUT changes associated with each treatment group during the time course are shown in Figures 1-4. Statistical analysis revealed no significant difference between the NITBUT at 30, 60, and 90 min compared with the baseline value for PBS and PFT treatment [Figures 1 and 2]. BAK treatment showed a positive time-dependent significant decline in NITBUT at 30 min (−2.18 s; $P < 0.05$), 60 min (−4.46 s; $P < 0.001$) and 90 min (6.28 s; $P < 0.001$) while a significant decline in the BPT treated group was only found at 90 min (3.52 s; $P < 0.001$) as shown in Figures 3 and 4.

Results showing NITBUT values among the treatment groups at each time point are shown in Figure 5. Data analysis revealed no significant differences in NITBUT values between the treatment groups at baseline ($P > 0.05$; one-way ANOVA). At 30 and 60 min posttreatment, only the BAK-treated group showed a significant reduction in NITBUT (−1.19 s; $P < 0.001$ and − 4.43 s; $P < 0.001$, respectively) compared to the PFT-treated group. At 90 min posttreatment, NITBUT was significantly low in both the BPT (−3.95 s; $P < 0.001$) and BAK (−6.29 s; $P < 0.001$) treated groups.

DISCUSSION

Results of measurement of tear stability using noninvasive techniques have been variable.[17,22-24] A study by Mengher *et al*.[17] on Caucasian subjects reported NITBUT values (>47.9 s) that were more than twice that observed in this study (19.98 ± 4.61 s). Studies have attributed this disparity to race,[25] age,[26] and different types of instruments used in the studies.[27] However, our result is comparable to that reported for Hong Kong-Chinese subjects (16 ± 9.4 s)[28] and another population of black subjects (15.3 ± 3.0 s),[29] which also used a noninvasive technique on a similar age range (20–32 years). Nevertheless, it remains uncertain as to what extent this difference might be explained by age and type of instrument.

Our results showed a significant difference in mean NITBUT values for the different treatments, which was found to be related to the preservative (0.01% BAK). The application of BPT did not result in a significant decline in the NITBUT

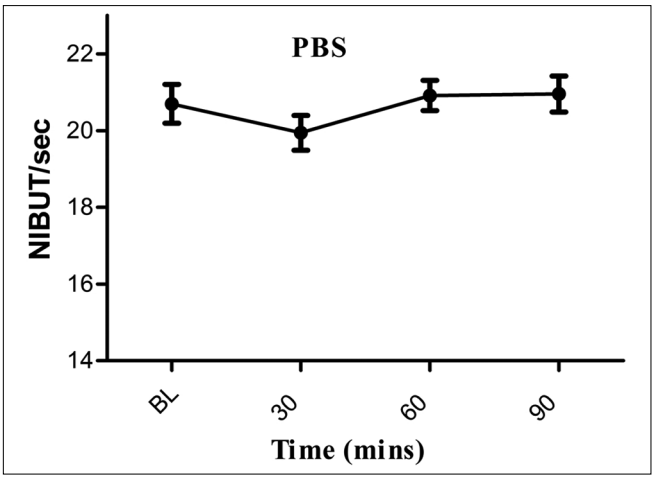

Figure 1: Effect of phosphate buffered saline (PBS) on noninvasive tear breakup time (NITBUT)

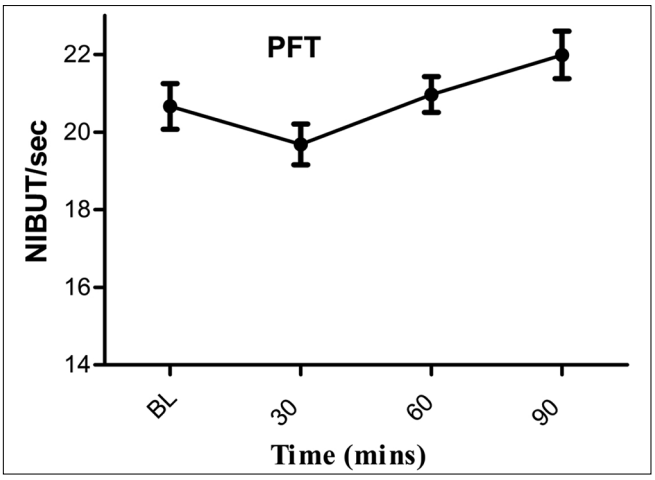

Figure 2: Effect of preservative-free timolol (PFT) on noninvasive tear breakup time (NITBUT)

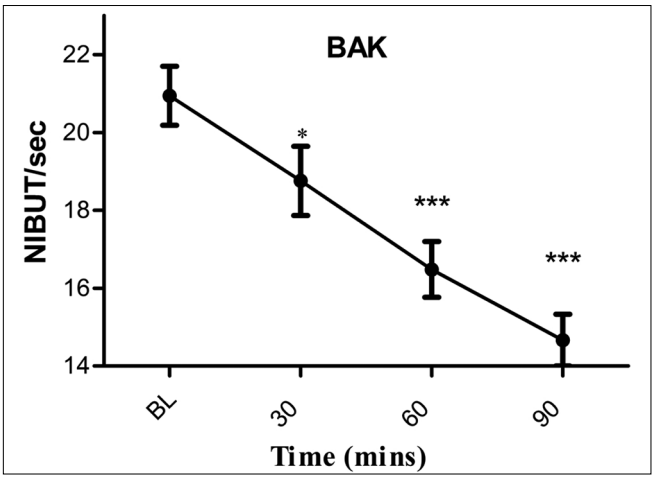

Figure 3: Effect of benzalkonium chloride (BAK) on noninvasive tear breakup time (NITBUT). *P<0.05, ***P<0.001

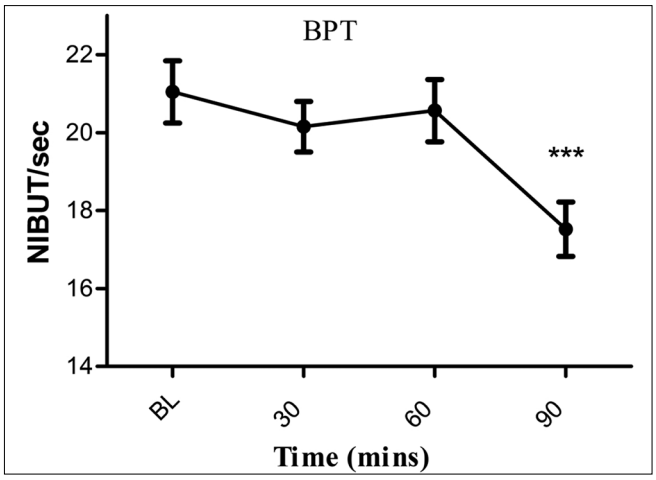

Figure 4: Effect of benzalkonium chloride preserved timolol (BPT) on noninvasive tear breakup time (NITBUT). *P<0.05

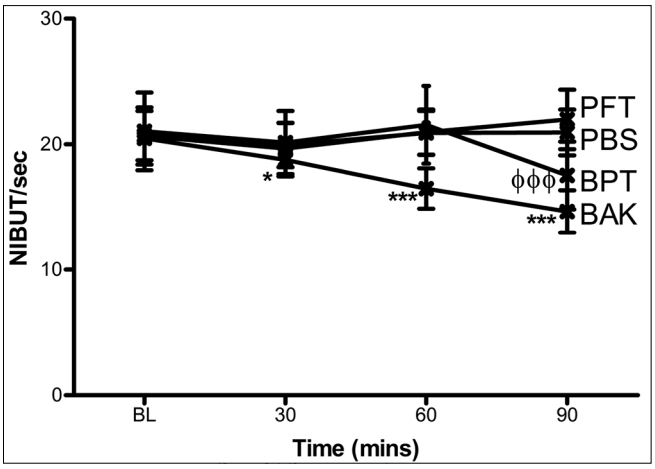

Figure 5: Comparison of the effects of different topical treatments (phosphate buffered saline (PBS), benzalkonium chloride (BAK), BAK preserved timolol (BPT) and preservative free-timolol (PFT)) on noninvasive tear breakup time (NITBUT). Analysis was performed using the One-way ANOVA followed by Dunnett's multiple comparison post hoc test.PFT vs BPT: ϕϕϕϕϕP< 0.001; PFT vs BAK:***P<0.001

until 90 min whereas NITBUT after application of BAK alone reduced rapidly at 30, 60, and 90 min. In contrast, no significant changes were observed in the PFT and the phosphate buffer saline as their NITBUT values maintained a level not significantly different from baseline at all time points. Therefore, it is conceivable that the reduction in NITBUT of the BPT and BAK only solutions was due to the presence of BAK in both solutions. These findings confirm earlier reports that BAK alone or in combination with timolol decreased the stability of the preocular tear film.[30,31] The most likely mechanism of this effect is that BAK, quaternary ammonium, has detergent properties[11] and, therefore, can disrupt the tear lipid layer further enhancing tear evaporation. In addition to its effect on the lipid layer, studies have observed that it exerted cytotoxic effects on epithelial cells and the microvilli of the corneal apical epithelial cells.[32] The microvilli increase the ocular surface area for tear adherence,[33] the quality of these surfaces being an important determinant of tear film stability since the tear film is anchored to them.

The more rapid decline in tear film stability after installation of BAK alone compared to the BPT suggesting that the harmful effect of BAK on tear film stability may be ameliorated when in combination with timolol. This observation is noteworthy as it may indicate a plausible role of unpreserved timolol in the improvement in tear stability. This confirms findings by Terai *et al.*[30] that the decline in tear stability following treatment with BAK alone was significantly higher (40%) compared to BPT (16%).

To the best of our knowledge of the authors, this study is the first which investigated the effect on tear film stability of PFT, preserved timolol and the preservative alone in parallel, taking into account that some investigators[14] observed decline in tear film stability after application of PFT in the eye of their subjects while others did not.[31] In this study, PFT clearly did not show any significant decline in NITBUT. These inconsistencies may be accounted for by the difference in study design and techniques used in assessing tear stability. For example, the Kuppins study which showed a reduction in NITBUT after application of PFT may have been influenced by the cross-over study design employed, whereby subjects previously administered with BAK-containing timolol solution were later administered PFT. Further, most of the previous studies in literature have used the invasive tear breakup time to assess tear stability.

Consistent with the findings of Trees and Tomlinson,[34] we also found an initial decrease in NITBUT, compared to baseline, occurring within 30 min of installation of all the four topical solutions although this was not statistically significant. Our data, therefore, provides further evidence in support of the report by a previous study, that an initial tear film instability is produced by the installation of any ophthalmic solution administered topically on the eye.[35] This instability is attributed to the increased fluid volume within the eye, the initial tear volume (7 μl),[36] being increased by a factor of 7 due to the instillation into the conjunctival sac of one drop (40 μl)[37] of fluid. This disrupts the lipid layer of the tears, thereby causing excessive tear evaporation rate.[34] Thus, it would seem prudent to leave an interval of 30 min time after instilling a diagnostic eye drop before assessing the tear film when conducting a clinical investigation. However, the decrease in NITBUT for the PFT and PBS was transient and rapidly returned to baseline.

We acknowledge the major limitation of this study to be the fact that we investigated short-term effect of the timolol formulations on tear stability only in healthy subjects using only a single drop instillation at 1 time point. This limits extrapolation of our results to patients with glaucoma who require lifelong drop application of

antiglaucoma medications. The short-term effect of these formulations may not reflect the long-term effects of chronic glaucoma medications. It is possible that several months of administering PFT could have similar effects on tear film stability as BPT. Longitudinal studies in this area are recommended. Nevertheless, the results of our study in young and healthy subjects are also relevant in decision-making in the management of glaucoma patients.

CONCLUSION

BPT is associated with a significant decline in tear film stability in Africans. This finding has implications in the management of glaucoma in patients with high-risk of dry eyes.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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