

## A comparative study of benzalkonium chloride-free latanoprost versus benzalkonium chloride-preserved latanoprost on ocular surface health in patients of primary open angle glaucoma

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### ABSTRACT

**Background:** Prolonged use of anti-glaucoma therapy leads to development of ocular surface disease (OSD). The purpose of this study was to compare the effect of Benzalkonium chloride (BKC)-free latanoprost and Benzalkonium chloride (BKC)-preserved latanoprost on ocular surface health in patients of primary open angle glaucoma (POAG).

**Methods:** This was a prospective, open-label, randomized, interventional, switch trial. 30 established cases of POAG who were already on BKC-preserved latanoprost for atleast more than three months were enrolled. Their Schirmer test and Tear film break-up time (TBUT) were recorded at the baseline. They were required to answer an ocular surface disease index (OSDI) questionnaire from which an OSDI score was calculated. They were switched to BKC-free latanoprost for another three months. On their follow-up visit at 6 weeks and 12 weeks, Schirmer test and Tear film break up time were performed again and OSDI score was calculated.

**Results:** Schirmer test increased from  $6.73 \pm 3.77$  mm at baseline to  $9.53 \pm 3.67$  mm at 6 weeks and  $11.97 \pm 3.53$  mm at 12 weeks ( $p=0.001$ ). Mean TBUT improved significantly from  $6.77 \pm 3.82$  seconds at baseline to  $8.63 \pm 3.91$  seconds at 6 weeks to  $10.47 \pm 3.76$  seconds at 12 weeks ( $p=0.001$ ). OSDI score decreased from  $31.55 \pm 23.32$  at baseline to  $23.42 \pm 21.93$  at 6 weeks to  $15.82 \pm 20.10$  at 12 weeks ( $p=0.001$ ).

**Conclusions:** BKC-free latanoprost led to improvement in tear film status or ocular surface health of glaucoma patients as compared to BKC-preserved latanoprost.

**Keywords:** Benzalkonium chloride, Dry eye, Glaucoma, Latanoprost, Ocular surface disease, Preservative free

### INTRODUCTION

Glaucoma, a vision debilitating disorder has become the second leading cause of blindness worldwide.<sup>1</sup> Topical medications are the crux of anti-glaucoma therapy.<sup>2</sup> Preservatives form an essential ingredient of these topical medications as they prevent microbial contamination and maintain their efficacy.<sup>3</sup> Benzalkonium chloride (BKC) is reigning the ophthalmic industry since 1940s bagging the tag of most commonly used preservative.<sup>4</sup> However the long-term use of BKC has been found to be hazardous.<sup>5</sup> It has dose-dependent effects.<sup>6</sup> It damages the tear film and activates the production of inflammatory mediators.<sup>7,8</sup>

The main purpose of our study was to compare the effect of BKC-free latanoprost versus BKC-preserved latanoprost on ocular surface health in patients of primary open angle glaucoma (POAG) by means of parameters like Schirmer test, Tear film break up time (TBUT) and ocular surface disease index (OSDI) questionnaire.

### METHODS

The study was conducted at Out Patient Department (OPD), Department of Ophthalmology, Government Medical College and Rajindra Hospital, Patiala, Punjab. This was a prospective, open-label, randomized, interventional, switch trial. The trial was registered at the

Clinical Trial Registry- India [CTRI.nic.in identifier: CTRI/2016/06/007001] and the World Health Organization [Universal Trial Number: U1111-1165-4913].

After obtaining approval from Institutional Ethics Committee (IEC), patient recruitment was started. Written informed consent was taken from all patients. Thirty established cases of POAG who were already on BKC-preserved latanoprost for atleast more than three months were enrolled. Their chief complaints, medical history and past ocular history were taken. Patients with past history of any ocular surgery in last one year, intake of any medication causing dry eye, patients suffering from rheumatoid arthritis, scleroderma or any other disease where dry eye is one of the manifestations, history of any ocular trauma in last three months, concomitant conjunctivitis, keratitis or uveitis and patients using contact lens during the study time period were excluded. Schirmer test was performed by using Schirmer tear test strips. Strip was carefully removed and kept in the lateral part of lower conjunctival sac of patients for about five minutes and then the length of the wet area was recorded. Schirmer test reading more than 10 mm was considered to be normal.<sup>9</sup>

For Tear film break up time, diagnostic ophthalmic sterilized fluorescein sodium strips were used. Strip was moistened with sterile ophthalmic solution or saline and its tip was placed on bulbar cornea. After the tear film took a uniform fluorescent green appearance, patient was instructed not to blink for the next 60 seconds. Time between one complete blink and appearance of first dark spot was taken as TBUT. TBUT reading more than 10 seconds was taken to be normal.<sup>9</sup>

Patients were required to answer an OSDI questionnaire which is basically a “12-item” questionnaire based on ocular complaints of the patient in the past one week. OSDI score ranges from 0 to 100. OSDI score  $\leq 12$  was taken to be normal.<sup>10</sup> After performing Schirmer test, Tear film break up time and calculation of OSDI score, patients were switched over to BKC-free latanoprost for another three months. At 6 and 12 weeks of follow-up, Schirmer test, Tear film break up time and calculation of OSDI score were performed again.

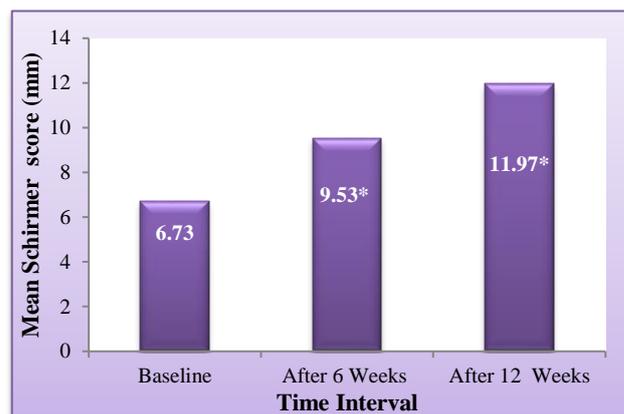
Statistical analysis was performed using SPSS software version 20.0 Chicago, Illinois, USA. For analysis of quantitative data, paired t test was used. For categorical variables and qualitative data, chi square test was used. The results were finally presented in tables, charts and bar diagrams. p value less than 0.05 was considered as significant (S) and less than 0.01 was considered as highly significant (HS).

## RESULTS

A total of thirty POAG subjects who were on BKC-preserved latanoprost for atleast more than three months

were enrolled at the baseline and then they were switched over to BKC-free latanoprost for another three months. Maximum number of patients were in the age group of 61-70 years. The mean age of presentation was  $66.9 \pm 10.56$  years. A male preponderance in glaucoma patients was seen in the study (n=23; 76.67%).

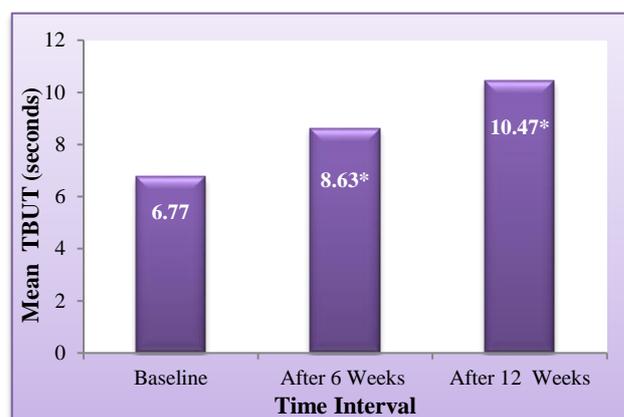
Mean value of Schirmer test increased from  $6.73 \pm 3.77$  mm at baseline to  $9.53 \pm 3.67$  mm at 6 weeks and  $11.97 \pm 3.53$  mm at 12 weeks (p=0.001 vs baseline) (Figure 1).



\*p=0.001

**Figure 1: Comparison of Schirmer test at baseline versus Schirmer test at 6 and 12 weeks.**

Mean TBUT improved from  $6.77 \pm 3.82$  seconds at baseline to  $8.63 \pm 3.91$  seconds at 6 weeks to  $10.47 \pm 3.76$  seconds at 12 weeks (p=0.001 vs baseline) (Figure 2).



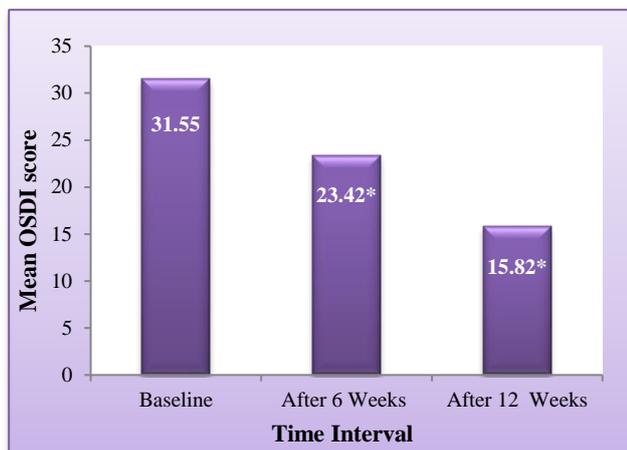
\*p=0.001

**Figure 2: Comparison of TBUT at baseline versus TBUT at 6 and 12 weeks.**

OSDI score decreased from  $31.55 \pm 23.32$  at baseline to  $23.42 \pm 21.93$  at 6 weeks to  $15.82 \pm 20.10$  at 12 weeks (p=0.001 vs baseline) (Figure 3).

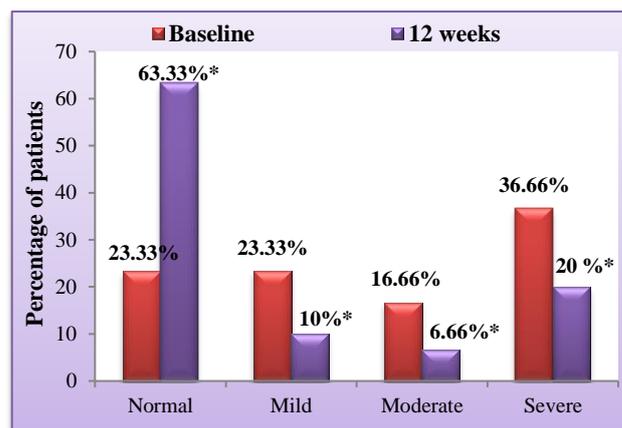
Percentage of glaucoma patients within each individual OSDI category (normal, mild, moderate and severe

ocular surface disease) differed from baseline to 12 weeks after initiating treatment with BKC-free latanoprost. There was an increase in the number of patients in normal category (23.33% to 63.33%), while a decrease was seen in mild OSDI (23.33% to 10%), moderate OSDI (16.66% to 6.66%) and severe OSDI (36.66% to 20%) category. p value was found to be 0.011, 0.001, 0.001 and 0.001 for normal, mild, moderate and severe OSDI category, respectively (Figure 4).



\*p=0.001

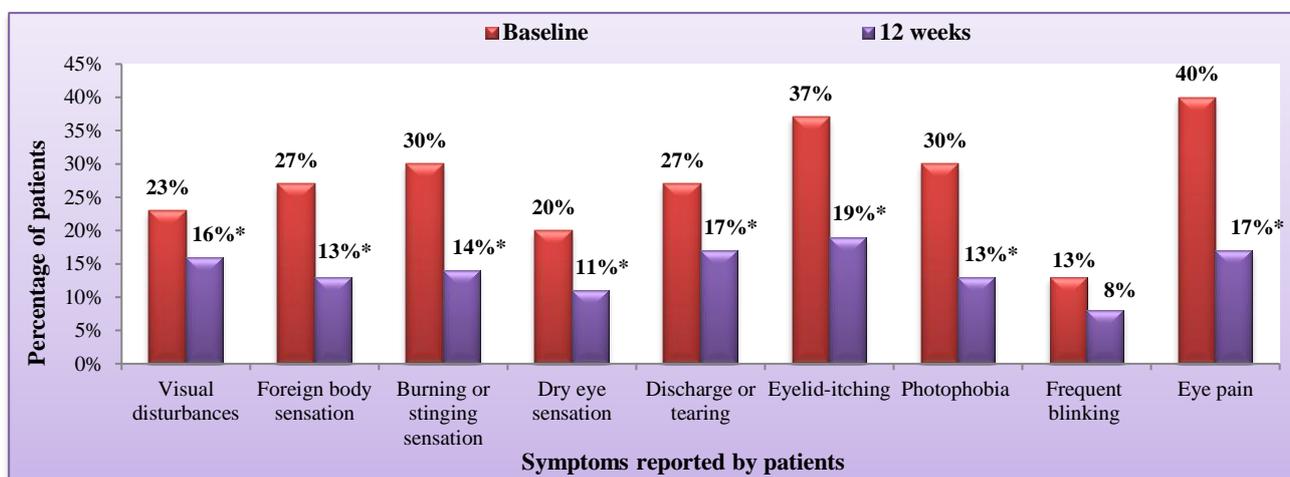
**Figure 3: Comparison of OSDI at baseline versus OSDI at 6 and 12 weeks.**



\*p=0.011, 0.001, 0.001 and 0.001 respectively

**Figure 4: Comparison of OSDI category at baseline versus OSDI category at 12 weeks.**

Eye pain was the most commonly reported symptom (40%) followed by eyelid-itching (37%), burning or stinging sensation (30%), photophobia (30%), foreign body sensation (27%), discharge or tearing (27%), visual disturbances (23%), dry eye sensation (20%) and frequent blinking (13%) at the baseline. A decrease in the frequency was reported at 12 weeks after switching to BKC-free latanoprost for every symptom. p value was found to be <0.05 for every symptom except frequent blinking (p=0.291) (Figure 5).



\*p<0.05

**Figure 5: Comparison of frequency of symptoms at baseline versus frequency of symptoms at 12 weeks.**

## DISCUSSION

Since long-term use of BKC has been implicated in causing OSD in glaucoma patients, the purpose of the present study was to compare the effect of Benzalkonium

chloride (BKC)-free latanoprost and Benzalkonium chloride (BKC)-preserved latanoprost on ocular surface health in patients of primary open angle glaucoma. In this prospective, interventional, open-label, randomized, switch trial, on substitution of BKC-preserved latanoprost eye drops with BKC-free latanoprost eye drops, there was

improvement in the mean score of Schirmer test from  $6.73 \pm 3.77$  mm at baseline to  $9.53 \pm 3.67$  mm at 6 weeks and  $11.97 \pm 3.53$  mm at 12 weeks ( $p=0.001$ ). There was statistically significant difference between mean Schirmer test value at both 6 and 12 weeks as compared to the baseline. Kuppens et al demonstrated reduced basal tear turnover rate in glaucoma patients on BKC-preserved medication as compared to those on BKC-free medication and Martone et al reported reduced Schirmer readings in glaucoma patients on preserved anti-glaucoma therapy as compared to those on preservative-free therapy.<sup>11,12</sup>

After switching treatment to BKC-free latanoprost, the mean TBUT improved from  $6.77 \pm 3.82$  seconds at baseline to  $8.63 \pm 3.91$  seconds at 6 weeks to  $10.47 \pm 3.76$  seconds at 12 weeks ( $p=0.001$ ). There was statistically significant difference between mean TBUT value at both 6 and 12 weeks as compared to the baseline. Uusitalo et al reported improvement in TBUT from 4.5 sec to 7.8 sec ( $p<0.001$ ) after switching therapy from BKC-preserved medication to BKC-free medication in glaucoma patients.<sup>13</sup> A significant difference was observed by Cvenkel B et al in TBUT between preserved medication group and untreated control group.<sup>14</sup>

The mean OSDI score decreased from  $31.55 \pm 23.32$  at baseline to  $23.42 \pm 21.93$  at 6 weeks to  $15.82 \pm 20.10$  at 12 weeks ( $p=0.001$ ). There was statistically significant difference between mean OSDI score at both 6 and 12 weeks as compared to the baseline. Katz et al and Walimbe et al demonstrated significant reduction in OSDI scores in glaucoma patients after switching treatment to BKC-free therapy from prior BKC-preserved prostaglandin therapy.<sup>15,16</sup>

### **OSDI category**

Replacing BKC-preserved latanoprost with BKC-free latanoprost, the percentage of glaucoma patients within each individual OSDI category (normal, mild, moderate and severe ocular surface disease) differed from baseline to 12 weeks after initiating treatment with BKC-free latanoprost. Statistically significant changes were observed in the normal OSDI category ( $p=0.011$ ), in the mild OSDI category ( $p=0.001$ ), in the moderate OSDI category ( $p=0.001$ ) and in the severe OSDI category ( $p=0.001$ ).

Martina et al observed a similar kind of shift in the number of patients in each OSDI category at final visit of 3 months as compared to the baseline in newly diagnosed patients of glaucoma who were put on BKC-preserved medication.<sup>17</sup>

### **Frequency of symptoms**

In our study, POAG patients reported ocular complaints at the baseline visit. Eye pain was the most commonly reported symptom (40%) followed by eyelid-itching

(37%), burning or stinging sensation (30%), photophobia (30%), foreign body sensation (27%), discharge or tearing (27%), visual disturbances (23%), dry eye sensation (20%) and frequent blinking (13%).

On comparison of frequency of symptoms reported by patients on BKC-preserved latanoprost at baseline and 12 weeks after starting treatment with BKC-free latanoprost, a decrease in the frequency was reported at 12 weeks. Statistically significant changes were observed for every symptom ( $p<0.05$ ) except frequent blinking ( $p=0.291$ ). Improvement in the frequency of symptoms with preservative free medication in glaucoma patients has also been reported by Pisella et al, Jaenen et al and Uusitalo et al.<sup>18-20</sup> Results of the present study were in accordance with the results of previously conducted studies.

The study has its own limitations accounting to its open-label design, lesser number of patients and shorter duration of follow-up.

### **CONCLUSION**

In a nutshell, the study concludes that BKC-free medications are indeed healthy for the ocular surface of glaucoma patients on long-term therapy as compared to BKC-preserved medications. BKC-preserved therapy deranges the tear film status of glaucoma patients and hampers their adherence to the treatment. It is therefore necessary to explore alternatives to BKC. Single Dose Units (SDUs) is an emerging option which has been launched already, however more horizons of research and development are required in the field of ophthalmic preservative industry.

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*Ethical approval: The study was approved by the Institutional Ethics Committee*

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