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OCULAR EFFECT OF PRESERVATIVE FREE AND BAK CONTAINING TRAVOPROST - A TERTIARY CARE HOSPITAL BASED STUDY

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ABSTRACT

Elevated intraocular pressure (IOP) is a leading risk factor for the development of primary open angle glaucoma, and reducing IOP is shown to be imperative to slow disease progression in this disease. Prostaglandin analogs showed advantages over other medical treatments and are presently the initial medication of choice. PGAs (latanoprost and travoprost) are typically administered in multi-dose bottles that contain preservatives to ensure sterility. Benzalkonium chloride (BAK, quaternary ammonium compound) is the most commonly used preservative in ophthalmic medications. Frequent dosing with benzalkonium chloride (BAK) containing ophthalmic solutions may lead to occular adverse effects. This study was done to evaluate and compare the effect of benzalkonium chloride (BAK) containing and preservative free ophthalmic solution of travoprost on ocular surface in patients with primary open angle glaucoma at regional institute of ophthalmology MotiLal Nehru Medical College Allahabad Uttar Pradesh. 47 newly diagnosed POAG patients were included in this prospective study. Patients were randomly divided in two groups. Patients in Group1 were treated with BAK preserved travoprost 0.004% and patients in Group 2 were treated with BAK free travoprost 0.004%. Intraocular pressure (IOP), hyperemia score and tear break up time (TBUT) were assessed at baseline, week 4 and 3 month after starting treatment.IOP decreased in all patients from baseline to 3month final visit (26.07± 2.48 mmHg versus 17.50 ± 1.79mmHg; $P < 0.0001$ for Group 1 and 25.20 ± 2.01 mmHg versus 16.92 ± 2.18 mmHg; $P<0.0001$ for Group 2).Hyperemia score for group1was increased (0.36±0.48 vs 0.76±0.67; p<0.003) at week 2 and statistically remained same for group 2 (0.38±0.36 vs 0.41±0.47; p= 0.640) at week 2. Mean TBUT decreased from 12.26±2.28seconds at baseline to 8.29±1.17seconds at 3month final visit (p<0.0001) for Group1. Mean TBUT decreased from 12.12±2.57 seconds at baseline to 11.75±2.33seconds at 3month final visit (p=0.053) for Group2. This study showed that BAK preserved travoprost 0.004% and BAK free are effective medication in newly diagnosed POAG patients. Long term use of BAK containing travoprost may negatively influence ocular surface health.

KEYWORDS: *Benzalkonium chloride, tear break-up time, hyperemia, POAG*

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INTRODUCTION

Glaucoma is a chronic eye disease and characterized by optic neuropathy and gradual visual field loss.According to WHO, It is the second most common cause of avoidable blindness after un operated cataract and third most common cause of visual impairment worldwide.The most prevalent form is primary open angle glaucoma (POAG), with almost 45 million sufferers worldwide. This number is expected to increase to 58.5 million by 2020[1-4]any clinical researches have shown that damage to the optic nerve in glaucoma is associated with elevated IOP.Decreasing IOP reduces both the incidence of glaucoma in individuals without optic nerve damage and the rate of new damage in individuals with glaucoma.[5-6]For several reasons, including easier accessibility compared with surgery and often similar outcomes regarding lowering in intraocular pressure IOP, medications remain the first line of therapy.[7]Medical therapy of the glaucoma includes β-blockers, α-2 adrenergic, carbonic anhydrase inhibitors and prostaglandin analogs (PGA).[8] Prostaglandin analogs showed advantages over other medical treatments and are presently the initial medication of choice. PGAs are able to decrease IOP by 33%, which is more effective than other group of drugs.There is a higher rate of adherence to treatment as these drugs require only once a day dosing.[9]Travoprost is approved as single drop once daily dose preparation in treatment of glaucoma.Prostaglandin analogs (latanoprost and travoprost) are typically administered from multi-dose bottles. Preservatives like benzalkonium chloride, chlorocresol, parabens etc. are regularly included in multi-dose ophthalmic solutions to ensure sterility.[10]Benzalkonium chloride (BAK, quaternary ammonium compound) is the most commonly used preservative in ophthalmic medications as a result of its broad-spectrum bactericidal and bacteriostatic activity at physiological pH.[11] Many experimental and clinical studies have suggested that the long term use of topical ophthalmic medication those containing BAK as a preservative, may induce changes of the ocular surface, tear film instability, epithelial apoptosis, conjunctival inflammation, fibroblast proliferation, corneal microvilli loss, and goblet cell loss in the conjunctival epithelium and manifest as decreased TBUT, increased ocular surface disease index (OSDI) score and hyperemia in medically treated glaucoma patients.[12-15] The concentration of BAK ranges from 0.004% to 0.02% in different ophthalmic solutions.[16]Now anti glaucoma eye drops that contain non-BAK preservatives and drugs without preservatives have become available.However, preparations with alternative preservative, manufacturing and packaging make this type of medications expensive and difficult to use for some patients.The goal of the current study is to compare the efficacy, safety, and tolerability of BAK containing and preservative free prostaglandin analogues travoprost in patientswith POAG.

MATERIALS AND METHODS

This was a prospective study performed in collaboration of the ophthalmology departments of MLN Medical College Allahabad and approved by the institutional ethics committee*(ECR/922/Inst/UP/2017)*.The patients included in the study signed a written informed consent.

Patients

Study was carriedout on the patients who attended outpatient department and glaucoma clinic at Regional Institute of Ophthalmology (R.I.O), Allahabad.Adult patients of either sex having primary open angle glaucoma were screened on the basis of selection criteria and those fulfilling the criteria were included in the study.

Inclusion criteria

It include both men and women aged ≥ 18 years with a diagnosed case of primary open angle glaucoma .They must be able to understand and follow study related advice.

Exclusion Criteria

Patientsnot willing to give consent, patients with chronic, recurrent or severe inflammatory eye disease, intraocular surgery,ocular trauma within the previous 6 months,ocular infection or inflammation or ocular laser surgery within the previous 3 months,clinically significant or progressive retinal disease or other severe ocular pathology and single functioning eye were not included in the study. Patients will also exclude if they are unable to discontinue all IOP lowering ocular medications before the study or hypersensitivity to prostaglandin analogues; or any abnormality preventing applanation tonometry in either eye. While patients of significant ophthalmic findings such as modified Shaffer angle grade < 2 in either eye,cup to disc ratio >0.8,severe central visual field loss and mean IOP> 36 mm Hg in either eye at any time point were also excluded .

Study instruments

- Topical ophthalmic solutions of PG analogues
- Slit lamp biomicroscope
- Direct ophthalmoscope

Methodology

The study consisted of 6 visits conducted during 2 sequential phases (i) the screening/eligibility phase, which included a screening visit, and (ii) the treatment phase, which included next 5 visits conducted at day 1, week 2, week 4, week 6 and week 12. At screening, patients discontinued use of all pre study medications, and the eligibility visit was scheduled after a predetermined washout period according to patient's pre study medication.At the eligibility visit, complete ophthalmic examination including best corrected visual acuity, hyperemia score, tearbreakuptime (TBUT), Goldmannapplanation tonometry, slit lamp biomicroscopy of the anterior eye segment and binocular indirect slit lamp fundoscopy was completed.Eligible patients were randomized in a 1:1 ratioand were started anti-glaucoma treatment after assigning group. Patientsassigned in Group1 were treated with BAK preserved travoprost 0.004%(*TRAVO, contains travoprost*0.004%*, preservative: benzalkonium chloride 0.02%; Micro lab limited Bangalore*) and patients in Group 2 were treated with preservative free travoprost 0.004%(*TOVAXO, contains travoprost*

0.004%, Ajanta pharma Ltd, Mumbai). Patients were instructed to instill 1 drop of their assigned drug in both eyes once daily in the evening at same time (±30 minutes) for 3 months, unless a safety issue prevented instillation. Safety and efficacy variables were assessed at selected time point (11 AM) during week 2, week 4, week 6, and week 12 study visits. One eye from each patient was chosen as the study eye, and only the study eye was used in the efficacy analysis. If only 1 eye of a patient was treated, that eye was selected as the study eye. If both eyes were treated, the worse evaluable eye was selected as the study eye. The worse eye was defined as the eye with the higher IOP at 11 AM across the eligibility visit. If IOP values were equal at 11 AM, the worse eye was defined as the eye with the higher IOP at 4 PM across the eligibility visit. Finally, if both eyes were equal at 4 PM, the right eye was selected for analysis. At subsequent visits, an interval medical history was obtained and any side effects were assessed, an ophthalmic examination including slit lamp biomicroscopy of the anterior eye segment, tear breakup time (TBUT) and Goldmannapplanation tonometry was performed.

Hyperemia

Bulbar conjunctival hyperemia observations were graded by a comparison with color photographic standards employing the following values: 0 = none (normal); 0.5 = trace (trace flush, reddish pink); 1 = mild (mild flush, reddish color); 2 = moderate (bright red color); and 3 = severe (deep, bright diffuse redness).[11]

Tear Break-Up Time (TBUT)

This is a method of determining the stability of the tear film and checking for evaporative dry eye. It was obtained by placing 5 µL of 2% preservative free sodium fluorescein to the inferior fornix using a fixed volume micropipette. To carefully mix the NaFl with the tear film, the patients were instructed to blink three times. The slit lamp was set at a magnification of 16X using cobalt blue illumination and a stopwatch was used to time the occurrence of the first break in the fluorescein stained tear film. The timer was started immediately after the last blink and stopped at the first break in fluorescein. This was measured three consecutive times and an average of these measurements was used to calculate the final TBUT. Despite the wide variation in TBUT among individual subjects, there is general agreement that a TBUT shorter than 10 seconds reflects tear film instability, whereas a TBUT shorter than 5 seconds is a marker of definite dry eye.[17]

Efficacy Assessment

This study consisted of a total of six visits, including screening visit. Assessments were conducted across five study visits at baseline, 2, 4, 6, and 12 weeks. The primary efficacy end point was decrease in mean IOP from baseline in the study eye, which was assessed 11 am ±30 minutes, at each study visit using Goldmannapplanation tonometry. Readings were collected in triplicate at intervals of 1 minute, and the mean value was reported. The same evaluator performed the IOP assessments and slit lamp examinations (using the same instrument) for each patient, whenever possible, for the duration of the study. Responder rates were also analyzed and assessed as the percentage of patients with IOP ≤18 mmHg on at least one time point.

Safety Assessments

Safety assessments consisted of evaluation of adverse events and vital signs. Best corrected visual acuity, dilated fundoscopy, automated perimetryand gonioscopy (screening visit only) were performed. In addition, specific ocular safety criteria included assessment of;

- Conjunctival hyperemia
- TBUT

STATISTICAL ANALYSIS

Sample size was calculated by assuming standard deviation of 3.5 mmHg. Minimum 22 evaluable patients in each treatment group was needed to evaluate difference of 1.5 mmHg in IOP between any two groups. A two sided, two sample Student's *t* test was used for quantitative data to evaluate significant difference between two groups and unpaired t-test for evaluation of quantitative data of same group (pre and post-intervantion). A significance level of 0.05 with power of 80% was tacken for calculation of sample size. All tests were two tailed, with a significance level of 0.05. All statistical analyses were performed using SPSS software version 20.

RESULTS

Patients Disposition

All 47 patients were randomized to receive treatment were considered as the safety population.The intent to treat population (all patients with baseline visit assessment who received at least one dose of study medication and at least one on therapy efficacy assessment) and per protocol population (patients with baseline visit assessment who received at least one dose of study medication and at least one on therapy efficacy assessment and no major protocol violation) consisted of 44 patients.

Demographic characteristics of patients

Gender distribution showed majority of the patients were male in each group. Group 1included 12 (52.7%) male, 11 (47.3%) female and Group 2 included 13 (54.2%) male, 11 (45.8%) female. It was seen that there was no statistical difference in number of male and female patients in groups as well as overall patients. The overall mean age of population was 43.61±11.38 (range 23 to 70). Mean age of patients in Group 1 and 2 was 42 ± 10.59 years and 43.66 ±11.29 years respectively. There was no statistically significant difference in mean age of different treatment groups (p=0.758). (Table -1)

Table 1
Demographic characteristics and basic Ophthalmologic parameters of newly diagnosed POAG patients

Category	Group 1	Group 2	Total
Sex			
Male	12(52.7%)	13(54.2)	25 (53.19%)
Female	11(47.3%)	11(45.8)	22 (46.8%)
Mean age (years)	42	43.66	43.61
SD	10.59	11.29	11.38
Range	25 to 66	25 to 65	23 to 70

IOP
Mean and SD of baseline IOP for treatment Group 1 and 2 was 26.07±2.48 and 25.2±1.91 mmHg respectively.Importantly there was no statistically significant difference in baseline IOP between the treatment groups (p=0.324).IOP decreased in all patients from baseline to 3month final visit (26.07± 2.48 mmHg versus 17.50 ± 1.79mmHg; *P* < 0.0001 for Group 1 and 25.20 ± 2.01 mmHg versus 16.92 ± 2.18 mmHg; *P*< 0.0001 for Group 2). (Table-2)

Table 2
Mean Intraocular pressure (in mmHg) of treatment groups at fallow-up visits

	Baseline (*Mean±SD)*	Week 2 (*Mean±SD)*	Week 4 (*Mean±SD)*	Week 6 (*Mean±SD)*
Group 1	26.07 (±2.48)	18.53 (±1.75)	18.06 (±1.75)	17.73 (±1.77)
Group 2	25.20 (±2.01)	18.00 (±2.06)	17.48 (±2.18)	17.18 (±2.17)

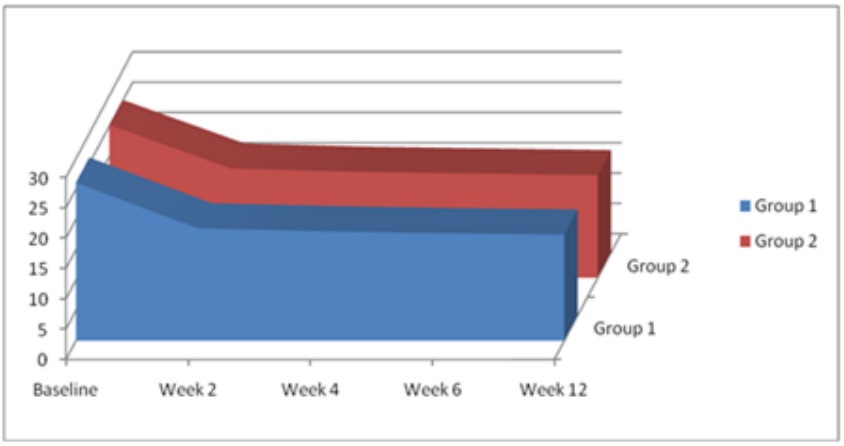


Figure 1
Change in IOP at different visits for group 1 & 2

We also observed the responder rate in terms of number of patients achieved IOP <18 mmHg at 12 week and found that it was comparable for each treatment groups. At the end of our study both the BAK free and BAK containing formulations of travoprost produced similar IOP response profiles. It was 52.17% for Group 1 and 56.52% for Group 2. (Table 3)

Table 3
Number and percentage of patients achieved IOP <18 mmHg at 12 wee

Groups	Number	%
Group 1	12 (22)	54.50
Group 2	13 (22)	59.00
Total	25 (44)	56.81

Hyperemia
Hyperemia scores were compared between groups at week 2. It was found that there was difference in scores between the groups at week 2. Difference was significant between Group 1 vs. Group 2 (p=0.041) at week 2. The differences were become insignificant at week 12 between groups (p=0.41 for group 1 vs 2) as well as from baseline value. (Table-4)

Table4
Mean Hyperemia score

	Group 1 (*Mean±SD*)	Group 2 (*Mean±SD*)
Baseline	0.36±0.48	0.38±0.36
Week 2	0.76±0.67	0.41±0.47
Week 12	0.43±0.51	0.32±0.36

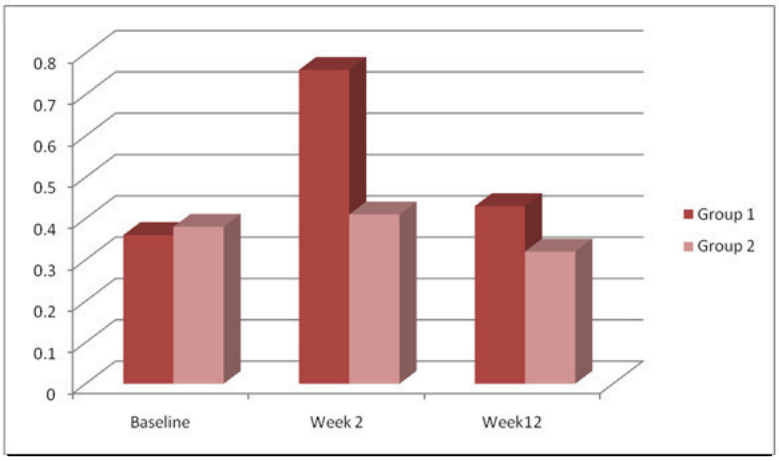


Figure 2
Change in hyperemia score at different visits for two groups

Tear Break-Up Time (TBUT)
Tear breakup time were noted at baseline, week 4 and week 12 visit to evaluate tear film instability in different treatment groups. Baseline TBUT of the treatment Group 1 and 2 were 12.26±2.28 and12.12±2.57 seconds respectively. Baseline values of TBUT were statistically similar for treatment groups (p =0.919).For treatment Group 1, TBUT decreased significantly at week 4 and week12 when compared with baseline mean value (p<0.0001) and there was also significant decrease in TBUT at week 12 when compared with week 4 (p<0.0001). For treatment Group 2 decrease in TBUT was insignificant at week 4 and week12 when compared with baseline mean value (p=0.680, p=0.053) and decrease in TBUT at week 12 when compared with week 4 was also insignificant (p=0.590). (Table-5)

Table 5
Mean TBUT (in seconds) of different groups at baseline and different visit

	Group 1 (*Mean±SD*)	Group 2 (*Mean±SD*)
Baseline	**12.26±2.28**	**12.12±2.57**
Week 4	**10.34±2.01**	**11.95±2.53**
Week12	**8.29±1.17**	**11.75±2.33**

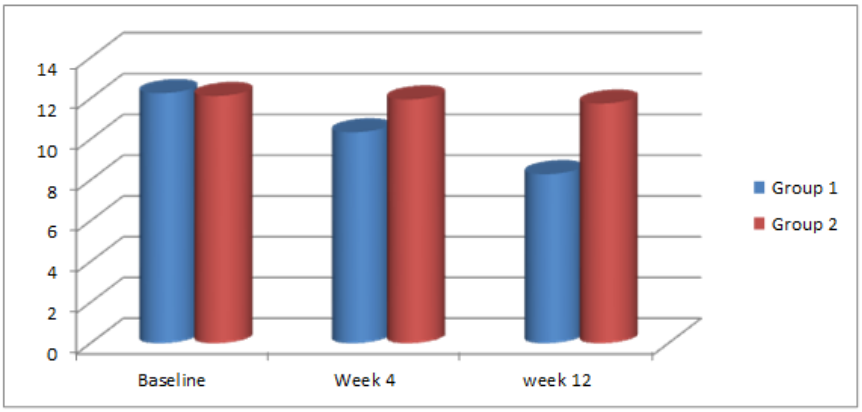


Figure 3
change in TBUT at different visits

TBUT was compared at week 4 and week 12. When TBUT was compared at week 4 and week 12, there was decrease in mean TBUT at week 4 and 12 in treatment Group 2. The decrease in TBUT was significant when compared with Group 1 ($p<0.024$ at week 4, $p<0.0001$ at week 12).

DISCUSSION

In the present study two prostaglandin analogues were evaluated, which differed in the type of preservatives and purpose of this study was to demonstrate whether a preservative free travoprost ocular solution would offer similar efficacy with better tolerability in comparison to BAK preserved travoprost. Both preparations provide similar IOP reduction throughout the study and met equivalence criterion. Decrease in IOP by 32% with both medications at the end of study.Maximum IOP lowering efficacy achieved after 2 weeks of treatment and maintained through three months for both preparations. Our results are in accordance with the results of previous studies.Gandolfi S *et al*., Study showed travoprost BAK-free is non-inferior to travoprost with BAK. Mean IOP reductions from baseline ranged from 7.6 to 8.7 mmHg in the travoprost BAK-free group and from 7.7 to 9.2 mmHg in the travoprost BAK group.[18]Statistical equivalence of BAK free and BAK containing preparation was also demonstrated by Lewis *et al*.. In a doublemasked, randomized, parallel group, multicenter, noninferioritystudy design showed mean IOP reductions, across all study visits ranged from 7.3 to 8.5 mm Hg for travoprost 0.004%without BAK and from 7.4 to 8.4 mm Hg for travoprost 0.004% with BAK.[19]A study done by P.A. Netland *et al*., showed that travoprost (0.004%) was equal or superior to latanoprost (0.005%) in lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension.[20] Parrish RK et al study showedlatanoprost, bimatoprost, and travoprost were comparable in their ability to reduce IOP in POAG and OH patients ($p=0.128$).[21]Meta analysis of randomized clinical trials reported, reduction of IOP in the range of 28% to 31% by latanoprost 0.005%, 29% to 31% by travoprost. In the study by Tomic *et al*., it was found that travoprost 0.004% dosed once daily in the evening provided good IOP control. It decreased IOP by 29.5% from 23.8±1.73 mmHg at baseline to 16.78±1.27 mmHg at 3 months after starting treatment.[22]Study of Maul E *et al*., showed treatment with travoprost 0.004% was associated with a significantly greater decrease from baseline in IOP compared with latanoprost 0.005%.Decrease in IOP by travoprost was 8.3 mmHg from baseline and for latanoprost it was 7.5 mmHg.[23]Conjunctival hyperemia also evaluated in our study (Physicians graded hyperemia) for all patients on a 0 to 3 scale at baseline, week 2 and final (week 12) visits. For group 1, there was statistically significant increase in scores were observed at week 2 (baseline vs week 2, $p=0.003$), but this difference became insignificant at week 12 visit (baseline vs week12 $p= 0.613$). These results correlate that hyperemia is associated with the use of BAK as preservative but the hyperemia was significant up to earlier part of therapy only and become insignificant at letter part of therapy. We found a significantly lower TBUT in the study patients at week 4 and week12, after starting the treatment with BAK preserved travoprost. Mean TBUT decreased from 12.26±2.28 seconds at baseline to 8.29±1.17seconds at 3month final visit ($p<0.0001$) for Group1. Mean TBUT decreased from 12.12±2.57 seconds at baseline to 11.75±2.33seconds at 3month final visit ($p=0.053$) for Group 2.In our study we also found that TBUT of BAK free and BAK containing formulations of travoprost was significantly different in all the visits.There was significant decrease in TBUT of BAK containing formulation of travoprost, suggests deleterious effect of BAK on TBUT. These findings are in accordance with some other studies. A study conducted by Henry *et al*., and showed that the baseline hyperemia scores were statistically different between latanoprost (0.7±0.7) and bimatoprost (1.0±0.9; $p<0.0001$). However, both groups experienced a significant decrease in hyperemia with travoprost BAK free (0.5±0.6 and 0.6±0.7 respectively; $p<0.0001$).[24] Crichton *et al*.,found that statistically significant differences in conjunctival hyperemia were seen among groups, from baseline to week 1 (0.04 [0.34] for bimatoprost with BAK, 0.20 [0.39] for travoprost BAK free, and 0.00 [0.42] for latanoprost with BAK; $P=0.018$). Pair wise t-tests were significant for travoprost versus both bimatoprost ($P=0.034$) and latanoprost ($P=0.007$), but not for bimatoprost versus latanoprost ($P=0.542$).[11]Ahmed *et al*.,did the study on thirty newly diagnosed primary open angle glaucoma (POAG) patients were treated with BAK free travoprost 0.004% and found that, hyperemia was reduced over the 3 month treatment period significantly from seven patients (23.3% at 6 weeks) to only one patient (3.3%) having mild to moderate degree of hyperemia at 12 weeks.[25]Ammar *et al*.,. found that BAK has significant in vitro cytotoxicity to cultured ocular epithelial cells. This toxicity of the prostaglandin analogs latanoprost, tafluprost and travoprost preserved with BAK was similar to the toxicity observed in their respective BAK concentrations.[26] In the study of T. Walimbe *et al*.,it was found that mean TBUT increased significantly from baseline (3.67±1.60 seconds) to 5.03±2.64 and 6.06±3.39 seconds after 28 and 56 days of treatment with BAK free latanoprost ($P<0.0001$).[2]Placebo or control group was not included in the study since it seemed unethical to leave the patients with glaucoma untreated for such a prolong period of 12 weeks.The current study did not include other prostaglandin analogues (eg. tafluprost or bimatoprost) as comparators. A limitation of the current study is that travoprost 0.003% and 0.004% was not compared with currently marketed travoprost formulations preserved with sofZia or polyquaternium1, or with other marketed prostaglandin analogues preserved with sofZia or polyquaternium1. Comparison of BAK containing PG analogues and preservative free PG analogues would enable direct assessment of the effect BAK on hyperemia rates and adverse event profiles. Another limitation of our study, we were not compared the effective preservation of BAK vs. BAK free preparations.

CONCLUSION

This study showed that both BAK preserved travoprost 0.004% and BAK free travoprost are effective medication in newly diagnosed POAG patients. Long

term use of BAK containing travoprost may negatively influence ocular surface health in sensitive patients.Therefore, while choosing the medication for glaucoma or ocular hypertension, both the efficacy and the tolerability of medication should be considered, especially in patients who already have ocular surface disease symptoms and clinical signs or who are at high risk of developing them due to use of BAK preserved medication.

CONFLICT OF INTEREST

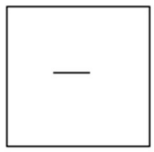
Conflict of interest declared none.

REFERENCES

1. Kaur IP, Lal S, Rana C, Kakkar S, Singh H. Ocular preservatives: associated risks and newer options. Cutaneous and ocular toxicology. 2009 Jan 1;28(3):93-103.
2. Walimbe T, Chelerkar V, Bhagat P, Joshi A, Raut A. Effect of benzalkonium chloride-free latanoprost ophthalmic solution on ocular surface in patients with glaucoma. Clinical ophthalmology (Auckland, NZ). 2016;10:821.
3. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. British journal of ophthalmology. 2006 Mar 1;90(3):262-7.
4. Friedman DS, Wolfs RC, O'Colmain BJ, Klein BE, Taylor HR, West S, Leske MC, Mitchell P, Congdon N, Kempen J. Prevalence of open-angle glaucoma among adults in the United States. Archives of ophthalmology (Chicago, Ill.: 1960). 2004 Apr;122(4):532-8.
5. Maier PC, Funk J, Schwarzer G, Antes G, Falck-Ytter YT. Treatment of ocular hypertension and open angle glaucoma: meta-analysis of randomised controlled trials. bmj. 2005 Jul 14;331(7509):134.
6. Webers CA, Beckers HJ, Nuijts RM, Schouten JS. Pharmacological Management of Primary Open-Angle Glaucoma. Drugs & aging. 2008 Sep 1;25(9):729-59.
7. Lichter PR, Musch DC, Gillespie BW, Guire KE, Janz NK, Wren PA, Mills MR, CIGTS Study Group. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. Ophthalmology. 2001 Nov 30;108(11):1943-53.
8. Van der Valk R, Webers CA, Schouten JS, Zeegers MP, Hendrikse F, Prins MH. Intraocular pressure–lowering effects of all commonly used glaucoma drugs: a meta-analysis of randomized clinical trials. Ophthalmology. 2005 Jul 31;112(7):1177-85.
9. Holló G. The side effects of the prostaglandin analogues. Expert opinion on drug safety. 2007 Jan 1;6(1):45-52.
10. Mohan K, Pravin S, Atul B. Ophthalmic microemulsion: a comprehensive review. Int J Pharm Bio Sci. 2012 Jul;3(3):1-3.
11. Crichton AC, Vold S, Williams JM, Hollander DA. Ocular surface tolerability of prostaglandin analogs and prostamides in patients with glaucoma or ocular hypertension. Advances in therapy. 2013 Mar 1;30(3):260-70.
12. Tomić M, Kaštelan S, MetežSoldo K, Salopek-Rabatić J. Influence of BAK-preserved prostaglandin analog treatment on the ocular surface health in patients with newly diagnosed primary open-angle glaucoma. BioMed research international. 2013 Jul 18;2013.
13. Schein OD, MUÑO B, Tielsch JM, Bandeen-Roche K, West S. Prevalence of dry eye among the elderly. American journal of ophthalmology. 1997 Dec 31;124(6):723-8.
14. Kaštelan S, Lukenda A, Salopek-Rabatić J, Pavan J, Gotovac M. Dry eye symptoms and signs in long-term contact lens wearers. Collegium antropologicum. 2013 Apr 22;37(1):199-203.
15. Leung EW, Medeiros FA, Weinreb RN. Prevalence of ocular surface disease in glaucoma patients. Journal of glaucoma. 2008 Aug 1;17(5):350-5.
16. Freeman PD, Kahook MY. Preservatives in topical ophthalmic medications: historical and clinical perspectives. Expert Review of Ophthalmology. 2009 Feb 1;4(1):59-64.
17. Savini G, Prabhawasat P, Kojima T, Grueterich M, Espana E, Goto E. The challenge of dry eye diagnosis. ClinOphthalmol. 2008 Mar;2(1):31-55.
18. Gandolfi S, Paredes T, Goldberg I, Coote M, Wells A, Volksone L, Pillai MR, Stalmans I, Denis P. Comparison of a travoprost BAK-free formulation preserved with polyquaternium-1 with BAK-preserved travoprost in ocular hypertension or open-angle glaucoma. European journal of ophthalmology. 2011 Dec;22(1):34-44.
19. Lewis RA, Katz GJ, Weiss MJ, Landry TA, Dickerson JE, James JE, Hua SY, Sullivan EK, Montgomery DB, Wells DT, Bergamini MV. Travoprost 0.004% with and without benzalkonium chloride: a comparison of safety and efficacy. Journal of glaucoma. 2007 Jan 1;16(1):98-103.
20. Netland PA, Landry T, Sullivan EK, Andrew R, Silver L, Weiner A, Mallick S, Dickerson J, Bergamini MV, Robertson SM, Davis AA. Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. American journal of ophthalmology. 2001 Oct 31;132(4):472-84
21. Parrish RK, Palmberg P, Sheu WP, XLT Study Group. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure:: A 12-week, randomized, masked-evaluator multicenter study. American journal of ophthalmology. 2003 May 31;135(5):688-703.

22. Tomić M, Kaštelan S, MetežSoldo K, Salopek-Rabatić J. Influence of BAK-preserved prostaglandin analog treatment on the ocular surface health in patients with newly diagnosed primary open-angle glaucoma. BioMed research international. 2013 Jul 18;2013.
23. Maul E, Carrasco FG, Costa VP, Casiraghi JF, Vargas E, Sarmina JS, Mayol R. A 6-week, multicenter, randomized, double-masked, parallel-group study comparing travoprost 0.004% to latanoprost 0.005% followed by 6-week, open-label treatment with travoprost 0.004%. Clinical therapeutics. 2007 Sep 30;29(9):1915-23.
24. Henry JC, Peace JH, Stewart JA, Stewart WC. Efficacy, safety, and improved tolerability of travoprost BAK-free ophthalmic solution compared with prior prostaglandin therapy. ClinOphthalmol. 2008 Sep;2(3):613-21.
25. Ahmed I. The noncorneal route in ocular drug delivery. DRUGS AND THE PHARMACEUTICAL SCIENCES. 2003 Mar 25;130:335-64.
26. Ammar DA, Noecker RJ, Kahook MY. Effects of benzalkonium chloride-preserved, polyquad-preserved, and sofZia-preserved topical glaucoma medications on human ocular epithelial cells. Advances in therapy. 2010 Nov 1;27(11):837-45.

Reviewers of this article



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