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Research Article

COMPARISON OF SAFETY OF LATANOPROST WITH PRESERVATIVE BENZALKONIUM CHLORIDE (BAK) VERSUS BAK-FREE TRAVOPROST IN PRIMARY OPEN-ANGLE GLAUCOMA

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ABSTRACT

Objective: The objective of this study was to compare the safety of BAK-preserved latanoprost versus travoprost BAK-free ophthalmic solution in the primary open-angle glaucoma (POAG).

Methods: Prospective, open-labeled, and randomized comparative study conducted in tertiary care hospital. Forty patients were enrolled and divided into 20 patients in each group: Group A topical latanoprost (0.005%) with BAK and Group B topical BAK-free travoprost (0.004%). Safety assessment was done by following parameters – Schrimer test (ST), tear break-up time (TBUT), and ocular surface disease index (OSDI).

Results: ST and TBUT were calculated at baseline, 1 month, 2 months, 3 months, and 4 months and OSDI scores were calculated at baseline, 2 months and 4 months. Group A and B were compared using ST, TBUT, and OSDI scores. Group B showed statistically significant results ($p<0.05$).

Conclusion: Topical BAK-free travoprost is more tolerable than BAK-preserved latanoprostin POAG.

Keywords: Primary open-angle glaucoma, Latanoprost, Travoprost, Benzalkonium chloride, Schirmer test, Tear break-up time, Ocular surface disease index.

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INTRODUCTION

Glaucoma is characterized by cupping of the optic disk and a specific pattern of irreversible visual field defects and loss of retinal ganglion cells that are associated frequently but not invariably with raised intraocular pressure (IOP) [1]. By 2010, almost 45 million people had primary open-angle glaucoma (POAG) worldwide, and this number will most likely increase to 111.8 million individuals in 2040 [2]. In India, the prevalence of glaucoma in the age group 40 years and above ranged from 6.9% to 8.1% [3].

Prostaglandin analogues (PGAs) are shown to be superior to older drugs in both efficacy and tolerability and have become the first-line therapeutic class for medical treatment of POAG worldwide. Long-term use of topical prostaglandin eye drops may induce ocular surface changes which cause discomfort and it has potentially negatively affected the compliance to the treatment. It is not clear that whether it is the active compound or the preservative that is involved in inducing such detrimental effect of ophthalmic solutions [4]. Addition of BAK (preservative) was necessary for preventing bacterial contamination of eye drops, so the majority of glaucoma medications still contain some levels of Benzalkonium chloride (BAK) [5]. Travoprost BAK-free ophthalmic solution is the first commercially available preparation of a prostaglandin analogue preserved without BAK [6].

Hence, this study was done to compare the safety of travoprost BAK-free ophthalmic solution to BAK-preserved latanoprost, as there is still dilemma about the safety of the use of prostaglandin with preservative and without preservative.

METHODS

This was an open-label and randomized prospective study conducted between February 2021 and January 2022 in tertiary care hospital after obtaining approval from the Institutional Ethics Committee (IEC) and written informed consent was taken. Patients of either sex more than 18 years of age, diagnosed as POAG and IOP >21 mmHg in both or either eye, were included in the study, while patients with any other ocular disease, already on other anti-glaucoma drugs, hypersensitive to prostaglandin analogue, history of intraocular surgery, history of any trauma to the eye within past 6 months, diabetes, hypertension or bronchial asthma, and pregnant and lactating women were excluded from the study.

After screening by Goldmann applanation tonometry, gonioscopy, fundus examination, and slit lamp examination, 40 newly diagnosed cases of POAG were enrolled, dividing into two Groups A and B, 20 each. Patients were allocated to receive one of the two different treatments for a period of 4 months and subjected to safety of drugs. Group A received latanoprost with BAK 0.005% ophthalmic solution once daily at fixed time in night and Group B received travoprost BAK-free 0.004% ophthalmic solution once daily at fixed time in night present from hospital supply. The patients were assessed for the safety issues at each visit, that is, Schirmer's test and tear break-up time (TBUT), at baseline, 1 month, 2 months, 3 months, and 4 months. Ocular surface disease index (OSDI) score was assessed for ocular dryness at baseline, 2 months and 4 months.

Clinical safety assessment tests

Schirmer's test (ST)

Schirmer's test uses paper strips inserted into eye for several minutes to measure production of tears. A small strip of filter paper is placed inside the lower eyelid. The eyes are closed for 5 min. The paper is removed and the amount of moisture is measured. Normal is ≥15 mm wetting of paper after 5 min, mild (14–9 mm), moderate (8–4 mm), and severe(<4 mm) [7].

TBUT

Tear film break-up time >10 s was taken to be normal, 5–10 s as marginal, and <5 s considered low. TBUT values were obtained by placing 5 µL of

2% preservative free sodium fluorescent dye to the inferior fornix and patients were asked to blink at least 3 times for proper mixing of the dye. The timer was started just after last blink and patient were instructed not to blink again; then, TBUT was recorded as the number of seconds that elapse between the last blink and the appearance of the first dry spot in the tear film. Final TBUT was calculated by averaging the three values [8].

OSDI

The index demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dry eye disease. The validated OSDI scores were classified as normal (0–12), mild ocular surface disease symptoms (13–22), moderate ocular surface disease symptoms (23–32), and severe ocular surface disease symptoms (33–100) [9].

Statistical analysis

Data are expressed as mean±SD. For intragroup and intergroup comparison, t-test and repeated measure ANOVA were applied. Bonferroni test was used for normally distributed variables. Safety assessment was done and percentages were calculated for qualitative data. $p<0.05$ was considered as statistically significant (Fig. 1).

RESULTS

Demographic data of the patients are shown in Table 1. The mean age was 49.3±11.43 years in the Group A and 46.2±14.5 years in the Group B, respectively, which were quite comparable. There was female predominance in Group A and male predominance in Group B.

In Group A, mean Schirmer test (ST) values at baseline,1 month, 2 months, 3 months, and 4 months were 15.7±0.65, 14.3±1.8, 11.85±3.51, 11.25±1.4, and 11.10±1.22, respectively. In Group B, ST values at baseline, 1 month, 2 months, 3 months, and 4 months were 15.95±1.11, 16.35±1.12, 16.5±0.97, 16.65±0.9, and 16.85±0.852, respectively (Fig. 2). On intragroup comparison, in Group A, there was a statistically significant reduction in mean ST values at all follow-up visits when compared to baseline, while, in Group B, there was a statistically significant increase in mean value at each follow-up visit as compared to baseline. On intergroup, comparison of ST values between Group A and Group B showed statistically significant results at all follow-up visits (*$p<0.05$).

In Group A, TBUT score at baseline and at the end of 1 month, 2 months, 3 months, and 4 months was 11.5±0.76, 11.35±1.137, 10.8±1.056, 10.40±1.231, and 9.05±1.276, respectively. In Group B, TBUT score at baseline and at the end of 1 month, 2 months, 3 months, and 4 months was 11.6±0.988, 11.5±1.051, 11.30±1.218, 11.15±0.988, and 11.25±1.196, respectively (Fig. 3). On intragroup comparison in Group A, there was a statistically significant reduction in mean TBUT score at the end of 4 months as compared to baseline, while, in Group B, results were statistically non-significant. On intergroup, comparison of

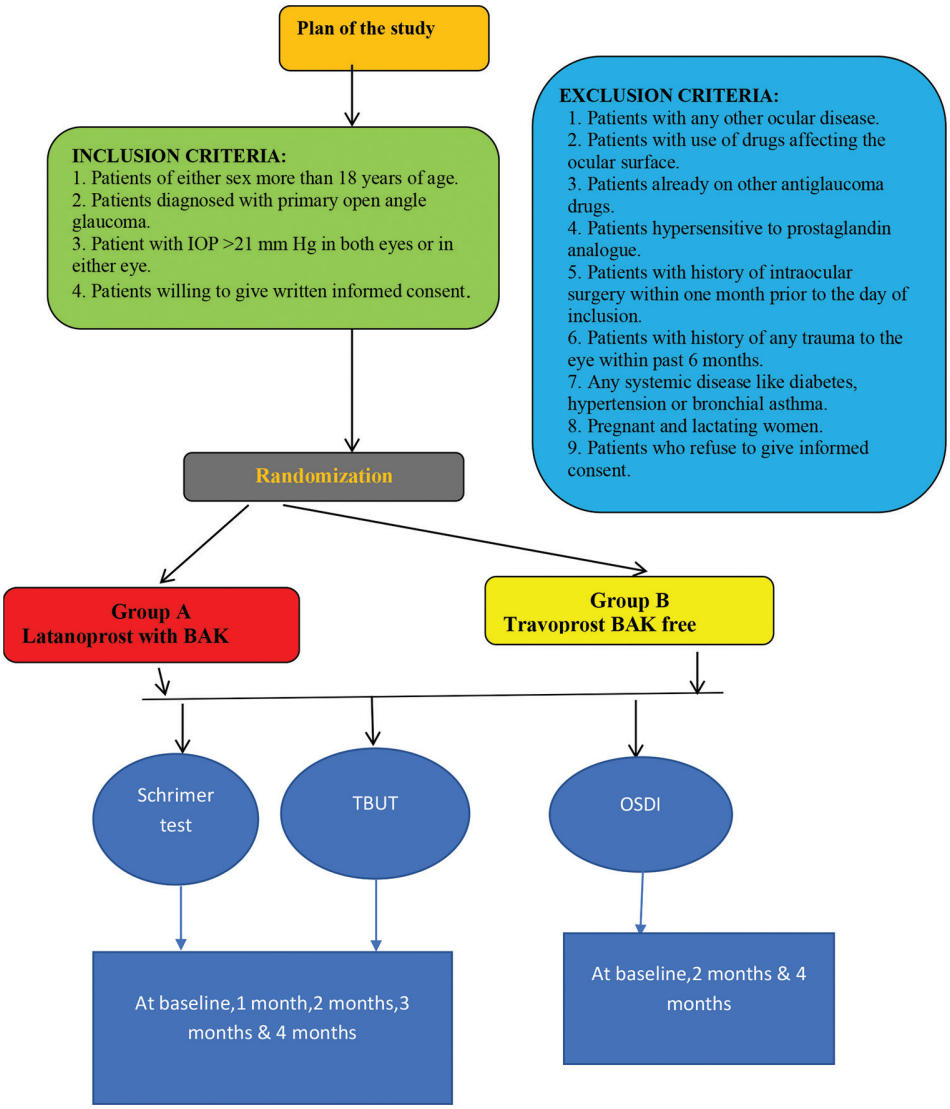

Fig. 1: Flowchart for study

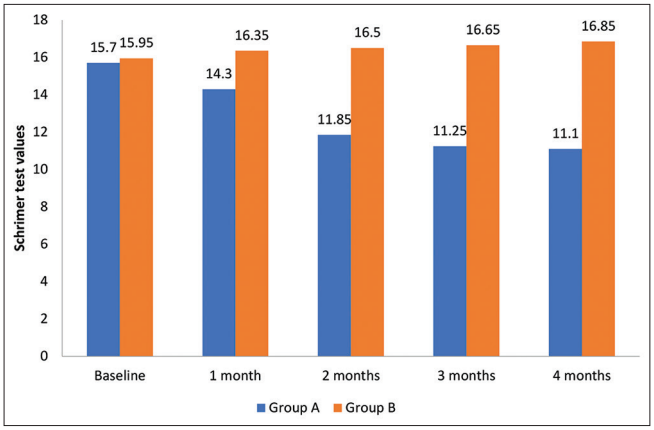

Fig. 2: Intragroup and intergroup comparison of Schrimer test values

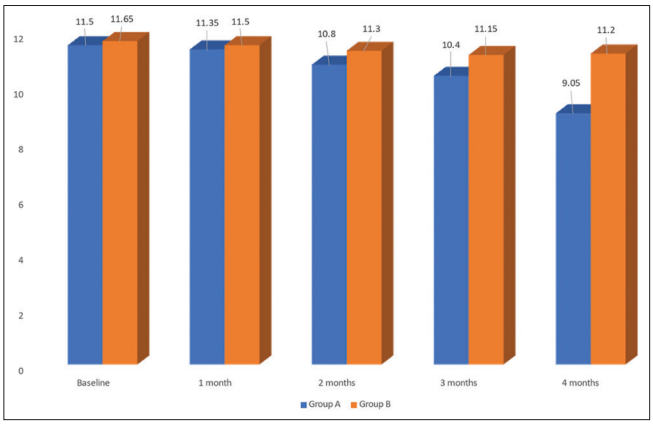

Fig. 3: Intragroup and intergroup comparison of tear break-up time values

Table 1: Demographic profile of study participants

Category	Group A	Group B
	Mean±SD	Mean±SD
Age in years	49.3±11.43	46.2±14.5
Gender		
Females	11 (55%)	8 (40%)
Males	09 (45%)	12 (60%)

TBUT between Group A and Group B showed non-significant results at baseline, 1 month, 2 months, and 3 months but statistically significant results at 4 months (*p<0.05).

In Group A, OSDI values at baseline, 2 months and 4 months, were 15.55±8.114, 17.6±7.163, and 18.25±8.391, respectively. In Group B, OSDI values at baseline, 2 months and 4 months, were 20.65±8.100, 14.25±3.932, and 10.55±4.501, respectively (Fig. 4). On intragroup, comparison in Group A showed statistically significant deterioration in mean OSDI score at the end of 2 months and 4 months as compared to baseline (**p<0.001). In Group B, there was a statistically significant improvement in mean OSDI score at the end of 2 months and 4 months as compared to baseline (**p<0.001). On intergroup comparison of OSDI between Group A and Group B, p value was not statistically significant at baseline and 2 months, while it was statistically significant at 4 months.

DISCUSSION

The management of POAG remains an area for never-ending research with better formulations and modalities continuously replacing

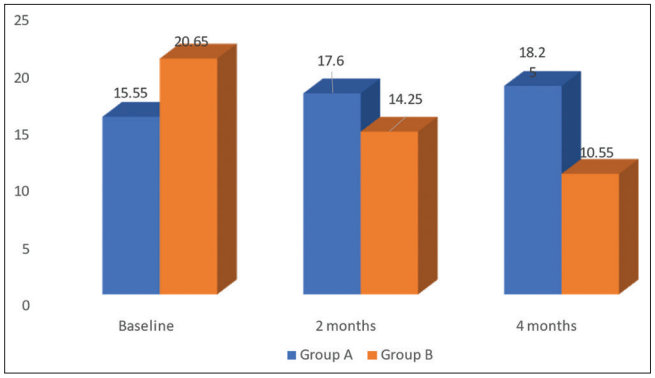

Fig. 4: Intragroup and intergroup comparison of ocular surface disease index scores

the present ones. PGAs have shown advantages over other medical treatments, and presently, they are initial medication of choice [3]. BAK, quaternary ammonium compound, is the most commonly used preservative in ophthalmic medications. Global reports have suggested that BAK-free preparations present with fewer adverse reactions as compared to BAK containing preparations [5].

In our study on intergroup, comparison of ST values between Group A and Group B showed statistically significant results at all follow-up visits (p<0.05). On intergroup, comparison of TBUT between Group A and Group B showed statistically significant results at 4 months (p<0.05). In Group B, it takes more time for the formation of dry spot. Chhabra *et al.,* in 2017, conducted a prospective, open-label, randomized, interventional, and switch trial to compare the effect of BKC-free latanoprost and BKC-preserved latanoprost on ocular surface health. ST increased from 6.73±3.77 mm at baseline to 9.53±3.67 mm at 6 weeks and 11.97±3.53 mm at 12 weeks (p=0.001). Mean TBUT improved significantly from 6.77±3.82 s at baseline to 8.63±3.91 s at 6 weeks to 10.47±3.76 s at 12 weeks (p=0.001). That is, it shows that in BAK-free preparations, there was increase in ST values suggesting improvement in dryness symptoms [10]. TBUT findings also very well correlate with the findings of our study. In our study on intergroup, comparison of OSDI between Group A and Group B, p value was statistically significant at 4 months, there were highest OSDI scores seen in Group A and lowest OSDI scores in Group B at 4 months. Jayanthi *et al.* conducted a study to compare the efficacy, safety of topical BAK-free travoprost 0.004% versus BAK-preserved travoprost 0.004% in patients with POAG. BAK-free travoprost demonstrated significantly lower OSDI scores (15.10±3.60) compared to BAK-preserved travoprost (23.47±7.10) at 12 weeks (p<0.0001) [6]. Moussa *et al.* (2016) had done a prospective and open-label study which evaluated and compared the efficacy of PGAs and determines the incidence of ocular surface disease in newly diagnosed, POAG patients were started on one of the PGAs latanoprost and travoprost (polyquad). The OSDI scores after 6 months treatment were 32.13 ± 24.10 for the latanoprost group and 10.68 ± 5.73 for the travoprost group. Statistically, the mean OSDI score of the group treated with travoprost was significantly inferior to the mean OSDI score of the other group. Travoprost was the most tolerated drug among the PGAs [11]. The results of the above two studies also correlate well with our study. Elimination or reducing exposure of BAK in ophthalmic solutions leads to improvement in tear film stability and also improves dry eye symptoms [12].

CONCLUSION

The findings of this study revealed preservative free eye drops show significant improvement in ocular surface health. Travoprost BAK-free like preparation may replace the preserved topical drugs in future.

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AUTHORS' CONTRIBUTIONS

Dr. Poojajuneja, Dr. Seema Rani, and Dr. Anupama Tandon have all contributed in development of protocol, conducting research, data collection, and statistics and authored the article. Dr. Garima Bhutani and Dr. Rahul Saini have done the editing, statistics, and designing and authored the article.

CONFLICTS OF INTEREST

Nil.

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