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Comparison of Safety of Latanoprost With Preservative Benzalkonium Chloride Versus BAKFree LatanoprostIn Primary Open AngleGlaucoma

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Abstract
Introduction
Glaucoma is a, silent killer of vision. Topical instilled drugs are the main crux of glaucoma therapy. Prostaglandin analogues (PGAs) include latanoprost, travoprost etc., as first-line medical treatment in glaucoma. Suggested in few studies, Benzalkonium chloride (BAK) is pro inflammatory and pro apoptotic molecule, leading to damage of tear film and changes in ocular surface. So, PGA molecule especially with BAK leads to decrease in adherence to prostaglandins.
Methods: *Prospective, open labelled, randomized comparative study conducted in Bhagat Phool Singh Government Medical College for Women, Khanpur Kalan. The study included two groups with 20 patients in each group , Group A topical latanoprost (0.005%) with BAK, Group B topical latanoprost (0.005%) BAK free. Schirmer test (ST) and Ocular surface disease index(OSDI)scores were calculated at baseline, 2months and 4 months.*
Results*: In group A, ST at baseline, 8 week and at 16 weeks were 16.75±2.07 mm,11.85±3.51mm,and 11.10±3.47mm respectively. In group B, ST atbaseline,8 week and at 16 weeks were,15.75+1.41 mm, 16.4+1.2mm, and 16.8mm respectively. Intergroup results compared at 2 months & 4 months, showed statistically significant results (p < 0.001). Intra group comparison done in group A from base line to 4 months showed statistically significant results (p <.001) but statistically significant results were not seen in group B. OSDI at baseline, 2 months and at 4 months in group A were 15.55± 8.1, 17.60± 7.1, and 18.25±8.39respectively. In group B, OSDI at baseline, 2 months and at 4 months were 18.65±3.7, 14.15±3.2, and 10.85 ± 3.4 respectively. Intergroup results compared at 4 months in both the groups showed statistically significant result(p < 0.05) . Intra group comparison done in both the groupsfrom baseline to 4 months, showed statistically significant results (p<0.001).*
Conclusion*: BAK-free latanoprost is more tolerable than BAK-preserved latanoprost.*

Keywords: *Primary open angle glaucoma (POAG) ; Latanoprost ; BAK; schirmer test; Tear break up time (TUBT); Ocular Surface Disease Index (OSDI)*

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I. Introduction:

Glaucoma, a chronic vision debilitating disease, has become the second main cause of irreversible blindness worldwide and third leading cause in India. As the patient remains asymptomatic for a long duration, it is commonly known as silent killer of vision. It was seen that glaucoma accounts for 5.8% of total blindness in India as surveyed in 1986-1989 by National Program for Control of Blindness- World Health Organisation (NPCB-WHO) [1] .In India, approximately 11.2 million people aged 40 years are having glaucoma, out of which 6.48 million are affected with primary open angle glaucoma (POAG)[2].

Topical instilled drugs are the main crux of glaucoma therapy. Prostaglandin analogues (PGAs) include latanoprost, travoprost, bimatoprost etc. , the first-line therapeutic class for medical treatment, preferred over other drugs because they do not have systemic side effects like bronchospasm, heart block, worsening of CHF and hypotension and ocular side effects itching, lid dermatitis, headache/brow and fluctuations in IOP[3,4].

Benzalkonium chloride (BAK) gained its importance in ophthalmology in 1940s as most popular preservative in many eye preparations as it prevents microbial contamination and maintain their efficacy [5,6]. But later on, BAK was found dangerous when used for a long time as it has dose dependent effects[7]. It is pro inflammatory and pro apoptotic molecule leads to damage of tear film and changes in ocular surface[8]. But, in clinical practice even though PGAs are very efficacious with satisfactory adherence, hypersensitivity reactions do develop to these topical drugs leading to frequent discontinuation of the therapy[6]. In some studies, it is seen these side effects are attributed to the preservatives used in conjunction with the PGA molecule especially BAK which leads to decrease in adherence to prostaglandins [9]. In this study, we have tried to analyze that safety issues of drugs are either because of the preservative or it is the active drugitself.

II. Methods:

The study was conducted by the Department of Pharmacology in collaboration with Department of Ophthalmology in Northern Indian Medical Institute after obtaining approval from the Institutional Ethics Committee. 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, any systemic disease , pregnant and lactating women were excluded from the study. Written informed consent was taken from all thepatients.

Treatment procedure: After screening by goldmann applanation tonometry, gonioscopy, fundus examination and slit lamp examination, 40 newly diagnosed cases of primary open angle glaucoma were recruited, dividing into two groups A and B, 20 each, patients were allocated to receive one of the two different treatments in an open fashion for a period of 4 months and subjected to safety of drugs. Group A received Latanoprost with BAK 0.005% ophthalmic solution once daily and Group B received Latanoprost BAK free 0.005% ophthalmic solution once daily present in hospital supply. All the patients were subjected to the examination at baseline, at the end of, 1month, 2 months, 3months and 4 months after starting treatment. IOP assessment was done using goldmann applanation tonometer. Visual field assessment was done by automated perimetry in both the eyes at the baseline and at final visit. Dilated fundoscopy was done at each visit. The patients were assessed for the safety issues at each visit i.e. Schirmer's test ,Tear break up time, Conjunctival hyperemia, iris pigmentation, Ocular surface disease index score and history of side effects on examination[10] .

Clinical safety assessmenttests:

1. Schirmer's Test(ST)[11]

Schimer'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 minutes. The paper is removed and the amount of moisture is measured. Normal is >=15mm wetting of paper after 5 minutes, mild (14-9 mm), moderate (8-4mm), severe(<4mm).

2. Tear break uptime(TUBT)[12]

Tear film break-up time >10 sec was taken to be normal, 5 to 10 seconds as marginal, and < 5 seconds 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 three 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.

3 .**Ocular Surface Disease Index (OSDI)** [13]

The index demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dry eye disease. The validated Ocular Surface Disease Index (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).

4. **Conjunctivalhyperemia**[14]

Bulbar conjunctival hyperemia observations was graded by a comparison with colour photographic standards employing :-0 = none (normal) ,0.5= trace (trace flash, reddish pink), 1=mild(mild flush , reddish colour),2= moderate(bright red colour) to 3 = severe (deep, bright diffuse redness)

5. **Iris pigmentation**[15]

Iris pigmentation grading was recorded with Boys-Smith lens grading before and after prostaglandin use. The area of hyperpigmentation was divided into three grades: Mild scattered-hyperpigmentation involving <1/3 of the area from limbus to pupil margin, Moderately scattered-hyperpigmentation involving > 1/3 but < 2/3 of the area from limbus to pupil margin and diffuse type.

6. **Other side effects:** Other safety issues are recorded by taking history as well as clinicalexamination.

STATISTICAL ANALYSIS

The data collected was tabulated and analyzed using Mean ± SD for quantitative data. Percentage and proportion for qualitative data. Student t- test and ANOVA for normally distributed variables to calculate mean difference with SSPS software. Safety assessment was done Chi square test and percentage . A p-value <0.05 will be considered as statisticallysignificant.

Observations and Results

A total of forty POAG subjects, 20 each group, Group A received Latanoprost with BAK 0.005% ophthalmic solution once daily and Group B received Latanoprost BAK free 0.005% ophthalmic solution once daily.

As depicted in table I, The mean age was 48 ±11.96 years in the group A and 50.2 ± 12.8 years in the group B (*P* = 0.167). Most of the patients belonged to the age group of 22-78 years in both the treatment groups. There were 9 (45%) male and 11 (55%) female patients in the group A and 11 (55%) male and 9 (45%) female patients in group B. The mean age of The M: F ratio was 1:1 and the socioeconomic status was 80% literate.

In table 2 Group A IOP at baseline was 25.7± 2.9mm and in group 2 was 26± 3.2 mm which was statistically insignificant (p>0.05). At 4 months in Group A was 20 ± 1.6 mm and in group B was 19.7 ± 1.12 mm which was statistically insignificant (p> 0.05). When both groups were compared at 4 months the difference was statistically insignificant (p>0.05).

In table 3 GQLI-15 (Glaucoma quality of life index)in Group A at baseline was 21± 3.84 and at 4 months was 19.45± 3.85 which is statistically significant (p< 0.001) and in Group B at baseline was 23.15± 5.14 and at 4 months was 19.3±3.70 which is statistically significant (p<0.001). Glare to bright light and increased dark adaptation were the most common symptoms and decreased gradually with treatment.

In both groups in our study the GQLI-15 after treatment at 4 months was statistically significant (p<.001)

In table 4 group A, ST values at baseline, 2 months and at 4 months were 15 ± 1.2 mm, 13.25± 2.0 mm, and 12.30±2.1mm respectively. In group B, ST value at baseline, 2 months and at 4 months 16.15±0.8 mm, 15.20±1.1 mm and 15.50±1.5mm respectively. When intra group analysis was done in both Group A and Group B at 2 months and 4 months from baseline, showed statistically significant result (p value < 0.05) in group A but not in Group B.When intergroup comparison done in both the groups at 2 months and 4 months, the difference was statistically significant.(p value<.001). It suggests dryness occur in group A but not seen in group B.

In table 5 TBUT value at baseline, 2 month and at 4 month in group A was 11.50 ±0.76 sec, 10.80 ± 1.05 and 9.05±1.2 sec respectively. In group B, TBUT value at baseline, 2 month and at 4 month was 11.60± 0.9 sec , 11.45±1.09 sec, and 11.25 ±0.9sec respectively. When intra group comparison done in both the groups at 2 months and 4 months from baseline, statistically significance (p <0.001) seen in group A but not in group B. In intergroup analysis, When the results were compared at 2 months and 4 months , showed statistically significant result (p value < 0.05) at 4 months but not in 2 months with measurable clinical improvement observed in TBUT in groupB.

Intable6 OSDIscoreingroupAatbaselinewas15.55±8.1to17.60±3.2at2monthsand18.25±8.3 at 4 months. In group B, OSDI score at baseline was 16.65±3.7 to 14.15±3.2 at 2 months and 14.85 ± 3.4 at 4 months.Whenintragroupcomparisondoneinboththe groups at2monthsand4monthsfrombaseline,

statistically significance ($p < 0.001$) seen in group A but not in group B. In intergroup analysis, When the results were compared at 2 months and 4 month, showed statistically significant result (p value < 0.05) at 4 months but not in 2 months with measurable clinical improvement observed in group B.

Conjunctival Hyperemia in group A, at baseline, 5% mild cases , at 2 months (5% trace, mild 60%) and at 4months (75% mild, 10% moderate). Total conjunctival hyperemia present was 85%. Conjunctival Hyperemia in group B, at baseline and at 1month was absent , at 2 months40% trace,at 3 months (40% trace,60% trace) and at 4 months 10% mild. Total conjunctival hyperemia present was70%.

III. Discussion.

Many PGAs have been marketed very commonly with preservative and without preservative but the preference of treatment of lowering the IOP i.e. the target pressure depending on initial reading at baseline, tolerability and adverse effects are main concern. But it has been seen in few studies that long-term use of topical medications in glaucoma may have negative impact on the ocular surface [10]. However, the mechanisms of ocular surface damage with PGAs is still not very clear. [6, 10, 19] Few studies reported that introduction of BAK containing eye drops was associated with an approximately twofold greater likelihood of developing OSD for each additional medication[8].

The results of our prospective, open labelled, randomized comparative clinical study demonstrate that the tolerability of drug is a key factor for use in POAG. Evidences show that long term use of drugs containing BAK causes dryness, inflammatory cell infiltration, blepharitis , superficial punctuate keratitis and eyelid eczema. [25,26,27,28,29]. In our study we evaluated the tolerability based on various parameters. Our study showed clinical improvement as well as statistically significant results both in schirmer test and TUBT. Studies conducted by Michael J Miyashiro et al 9 and the Horsley study, which reported a significant increase in tear breakup time after transition to BAK free molecule supporting the results of our study. The results of this study are consistent with Martina et al who observed a similar kind of shift in the number of patients in OSDI category at 12 weeks of visit as compared to baseline in newly diagnosed patients of glaucoma between BAK free and BAK present latanoprost [33] Katz et al and Walimbe et al also demonstrated significant reduction in OSDI scores in glaucoma patients with BAK free therapy than with BAK present therapy [31,32]

Hyperemia most common side effects of prostaglandin analogue was more common with latanoprost with BAK with a statistically significant association. Similar results shown by Tomic M et al, in his study about mild to moderate hyperemia within the week after starting the BAK containing IOP lowering topical agent.

There was a strong association between latanoprost and iris pigmentation and eyelashes growth both of which was more common in latanoprost with BAK. Similar results are also in literature. In our study Iris hyperpigmentation was 95% at 4 months of treatment with BAK latanoprost and 60% with BAK free latanoprost.It is noted that 3–10% of patients treated with latanoprost showed increased iris pigmentation after 3–4.5 months[37].

IV. Conclusion:

Latanoprost BAK free have a good control in lowering IOP suggesting the drug of choice to reach target IOP with monotherapy. Also, Latanoprost BAK free has been found to improve ocular surface damage and quality of life perception after a 4-monthfollow-up.
Further studies are needed to confirm this beneficial effect.

AUTHORS' CONTRIBUTIONS

The study was designed and conceptualized by Dr. Anupama Tandon, Dr Seema Rani and Dr Pooja Juneja Literature search, data acquisition, data analysis, and manuscript preparation were also done by them. Dr. Rahul helped in data analysis, manuscript preparation, manuscript editing, and manuscript review.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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Table 1:-Demographic parameters of newly diagnosed POAG patients.

Category	Group A	Group B	Total
Male	**09(45%)**	**11(55%)**	**20**
Female	**11(55%)**	**9(45%)**	**20**
Mean Age	**48±11.96**	**50±12.8**	**49**
Range	**23-78**	**25-80**	**23-80**

Table 2:-**IOP parameters of POAG patients**

	Baseline	1 month	2 month	3 month	4 month	Level of significance at 4 monthsintergroup
Group A	25.7±2.9	23.5±2.4	22.3±2.1	21.0±1.89	20.05±1.63	
Group B	26.0±3.2	23.5±2.25	22.05±1.9	21.1±1.61	19.7±1.12	p>0.05 Insignificant

Table 3 :- GQLI -15 Index in POAG

	Baseline	**4 months**	**Level of significance intragroup**	**Level of significance intergroup at 4 months**
Group A	**21±3.84**	**19.45±3.83**	**P<.001**	
Group B	**23.15±5.14**	**19.3±3.70**	**P<.001**	**P<.001**

Table 4:- Mean Schirmer score of two groups at different follow up visits

	Baseline	**2 months**	**4 months**	**Level of significance intragroup at 4 months**	**Level of significance intergroup at 4 months**
GroupA	**15±1.2mm**	**13.25±2.0mm**	**12.30±2.1mm**	**P<0.05**	
Group B	**16.15±0.8mm**	**15.20±1.1mm**	**15.50±1.5mm**	**p>0.05**	**P<.001**

Table 5:- TBUT parameters of two groups at different visits in seconds

	Baseline	**2 months**	**4 months**	**Level of significance between 2nd and 4th month (intragroup)**	**Level of significance (intergroup at 2nd and 4th month)**
GroupA	**11.50±0.76**	**10.80±1.05**	**9.05±1.2**	**P<0.001**	
Group B	**11.60±0.9**	**11.45±1.09**	**11.25±0.9**	**Not significant**	**At 2 monthsnot significant 4 months p<0.05**

Table 6:-OSDI parameters at different visits

	Baseline	2 months	4 months	**Level of significance between 2nd and 4th month (intragroup)**	**Level of significance (intergroup at 2nd and 4th month)**
Group A	15.55±8.1	17.60±3.2	18.25±8.3	P<0.001	
Group B	16.65±3.7	14.15±3.2	14.85±3.4	Not significant	**At 2 months not significant 4 months p<0.05**

Figure 1:- :- TBUT parameters of two groups at different visits in seconds

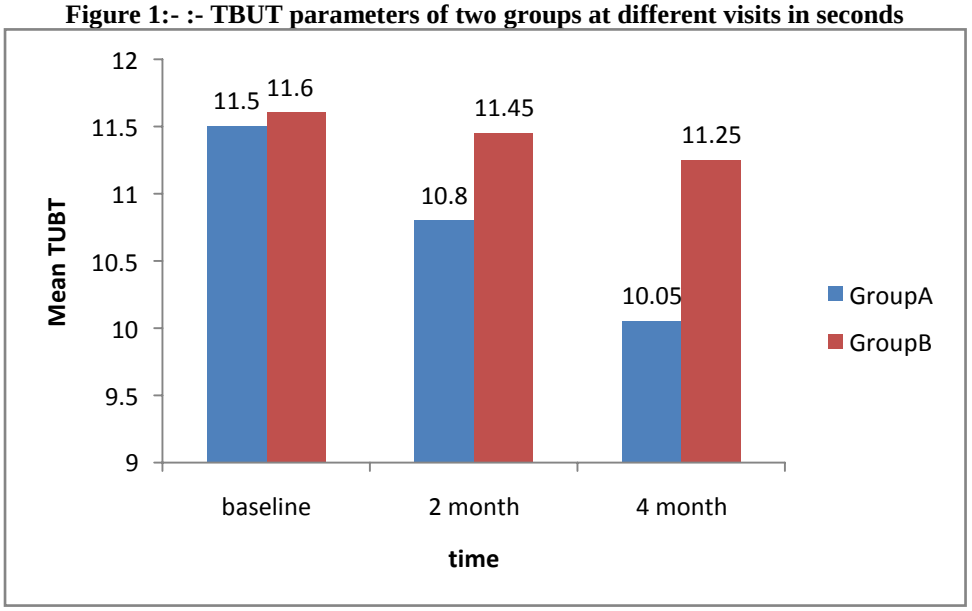
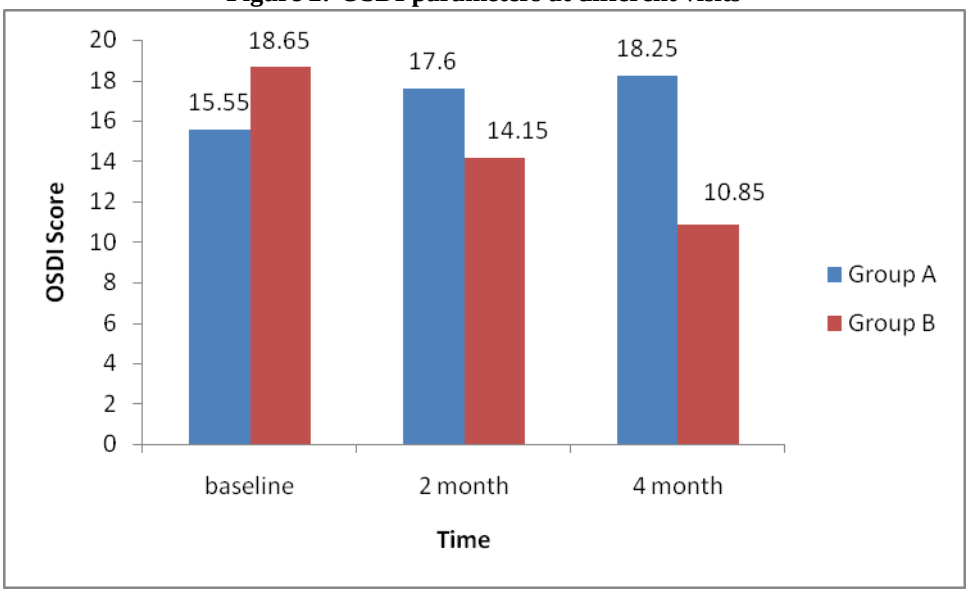


Figure 2:-OSDI parameters at different visits



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