Topical Prostaglandin Analogues with and without Preservatives on Tear Film Stability in the Long-Term Treatment of Glaucoma

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ABSTRACT

BACKGROUND

Prostaglandin analogues (PGAs) have proven to be the most potent of the anti-glaucoma medications in decreasing IOP, with little systemic side effects and hence are the initial treatment of choice. Many PGAs contain preservatives which are associated with increased ocular side effects, the most common preservative being benzalkonium chloride (BAK). BAK is known to cause cell toxicity and cell death in ocular surface tissues in a dose-dependent and time-dependent manner and often gives rise to ocular surface diseases, with the consequence of dysfunctional tear film in patients who are on long-term PGA therapy. We wanted to evaluate the long-term effects of prostaglandin analogue eye drops with and without preservative on tear film stability in glaucoma patients who are instilling these medications on a long-term basis.

METHODS

This is a prospective study conducted on 48 eyes from 48 patients of glaucoma and 30 eyes from 30 controls. Patients who were newly diagnosed to have glaucoma were started on either of the two eye drops: Tovaxo (Travoprost 0.004%, preservative-free) and 9PM (Latanoprost 0.005%, BAK 0.02%). The patients were followed up for one year at the end of which period Tear break up times (TBUT) were measured and Schirmer's tests were performed.

RESULTS

In preservative-free travoprost group 62.5% patients had TBUT between 6 and 10 seconds while BAK-preserved latanoprost group had 79.2% patients with TBUT between 6 and 10 seconds. 8.3% of patients in BAK-preserved latanoprost group had TBUT ≤5. The rest of the patients had normal TBUT (>10 seconds). 76.7% of the controls had a normal TBUT. None of the subjects in control and travoprost group had TBUT of 5 seconds or less. All patients in the travoprost group and all the controls had Schirmer test result >10 seconds while 91.7% of the patients in latanoprost group had TBUT >10 seconds. The intergroup difference was not statistically significant.

CONCLUSIONS

Long term instillation of prostaglandin analogues can be associated with tear film instability. BAK-preserved drugs may have a greater deleterious effect on the tear film than preservative-free drugs.

KEYWORDS

Preservatives, Tear Break Up Time, Tear Film Stability, Prostaglandin Analogue, Adverse Effects, Benzalkonium Chloride

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BACKGROUND

Clinical trials have shown that decreasing the IOP decreases the incidence and progression of visual field defect.[1,2] Treatment of glaucoma is hence aimed at lowering of IOP. Medical therapy with topical monotherapy is the first step in treating glaucoma as per the European Glaucoma Society Guidelines.[3] Among the topical anti glaucoma medications, prostaglandin analogues (PGA) have proven to be the most potent in decreasing IOP and with little systemic side effects and hence are the initial treatment of choice.[4,5] It is imperative for patients to be on medical treatment for lifelong. Many of the PGAs are known to have local side effects such as conjunctival hyperemia, stinging, dry eye, foreign body sensation; and they are of concern because these may have a negative bearing on the patients' compliance with the medication.[6] Many PGAs contain preservatives which are associated with increased ocular side effects, the most common preservative being benzalkonium chloride (BAK). BAK is a quaternary ammonium compound and exerts its antimicrobial effect by disrupting the cell membrane resulting in cell death of the organism. BAK is known to cause cell toxicity and cell death in ocular surface tissues in a dose-dependent and time-dependent manner and often gives rise to ocular surface diseases, with the consequence of dysfunctional tear film in patients who are on long-term PGA therapy.[7] The objective of this study was to explore the effects of Prostaglandin analogue eye drops with and without the preservative Benzalkonium chloride on tear film stability among glaucoma patients.

METHODS

This was a prospective study approved by the institutional ethics committee of the Faculty of Medicine, Aligarh Muslim University and was conducted in accordance with the Declaration of Helsinki and ethical guidelines. The analysis was conducted on 48 eyes from 48 patients of glaucoma and 30 eyes from 30 controls. 48 patients of glaucoma and 30 controls were enrolled for the study between December 2017 and July 2018 who had attended the ophthalmology OPD and the glaucoma clinic, Institute of Ophthalmology, Jawaharlal Nehru Medical College, AMU. The newly diagnosed patients of glaucoma who were started on prostaglandin analogues were recruited in the study. Patients who were newly diagnosed to have glaucoma were started on either of the two eye drops:

- Tovaxo (Travoprost 0.004%, preservative-free; Ajanta Pharmaceuticals)
- 9PM (Latanoprost 0.005%, BAK 0.02%; Cipla Pharmaceuticals)

Tovaxo has absolutely no preservative at all, while all other locally available preparations had some kind of preservative or the other in them. Very few brands of travoprost are there in the market which have BAK as preservative in them and are not readily available and hence not prescribed often. 9PM on the other hand is the most commonly prescribed brand of latanoprost and has a pretty high concentration of BAK in it. Hence, in order to compare the effects of BAK, these two medications made a prudent choice of combination for this study. Travoprost and Latanoprost are congeners, belonging to the same class of drugs with very little difference in structure and function and the effects of the individual drug molecule are similar. The two drugs in our study happen to be the most widely used drugs in their class and hence a significant difference in adverse effects between the two could bring a change in prevalent practice. Keeping the above facts in mind these two drugs were selected for this study. One eye of each patient was chosen randomly for inclusion in the study. The patients were followed up from the time of initiation of therapy and at the end of one year of follow up. Tear break up times (TBUT) were measured and Schirmer tests were performed.

Inclusion criteria for glaucoma patients were increased IOP, characteristic glaucomatous cupping, characteristic visual field loss on perimetry and evidence of glaucomatous damage to retinal nerve fiber and/or macular ganglion cell complex on OCT. Exclusion Criteria for glaucoma patients included use of eye drops other than prostaglandin analogues (Tovaxo or 9PM), history of ocular surgery, topical or systemic administration of antimicrobial agents in the past 2 weeks, suspected bacterial, fungal or viral infection, poorly controlled ocular or systemic disease. A group of controls were also included in the study who were normal healthy volunteers. Inclusion criterion for controls was no history of using any eye drops or systemic antimicrobial drugs within the last 12 weeks.

Statistical Analysis

The tear break up times and Schirmer test results were compared between latanoprost group, travoprost group and controls. A chi-squared test ($\chi 2$ test) was any statistical hypothesis test wherein the sampling distribution of the test statistic is a chi-squared distribution when the null hypothesis is true. Unpaired proportions were compared by Chi-square test. p-value ≤ 0.05 was considered as statistically significant.

RESULTS

The patients and controls were comparable in terms of age and sex. On performing post hoc test, for both the eyes, the difference in IOP between latanoprost and travoprost was not significant but the difference between controls and the PGA groups were significant. In travoprost group 62.5% patients had TBUT between 6 and 10 seconds while latanoprost group had 79.2% patients with TBUT between 6 and 10 seconds. 8.3% of patients in latanoprost group had TBUT ≤ 5. The rest of the patients had normal TBUT (>10 seconds). The intergroup difference was statistically insignificant.

	Latanoprost Group (with BAK)	Travoprost Group (without Preservative)	Control Group	p
Sex				0.37
Female	15 (62.5%)	12 (50%)	13 (43.3%)	
Male	9 (37.5%)	12 (50%)	17 (56.7%)	
Age (years)	57.54 ± 11.42	50.79 ± 10.47	52.23 ± 11.96	0.09
IOP RE (mmHg)	21.95 ± 2.80	21.83 ± 4.01	15.20 ±1.82	<0.0001
IOP LE (mmHg)	21.60 ± 2.57	22.50 ± 3.21	15.63 ± 2.05	<0.0001

Table 1. Patient Demographics and IOP of Both Eyes of the Patients and Controls

TBUT Grading (Seconds)	Latanoprost Group (with BAK)	Travoprost Group (without Preservative)	Total
≤5	2 (8.3%)	0 (0.0%)	2
6 to 10	19 (79.2%)	15 (62.5%)	34
>10	3 (12.5%)	9 (37.5%)	12
Total	24	24	48

Table 2. Mean TBUT in Travoprost and Latanoprost group

Chi-square value: 5.47; p-value: 0.06

TBUT Grading (Seconds)	Control Group	Latanoprost Group (with BAK)	Total
≤5	0 (0.0%)	2 (8.3%)	2
6 to 10	7 (23.3%)	19 (79.2%)	26
>10	23 (76.7%)	3 (12.5%)	26
Total	30	24	54

Table 3. Mean TBUT in Latanoprost Group

Chi-square value: 22.53; p-value: <0.0001

TBUT Grading (Seconds)	Control Group	Travoprost Group (without Preservative)	Total
≤5	0 (0.0%)	0 (0%)	0
6 to 10	7 (23.3%)	15 (62.5%)	22
>10	23 (76.7%)	9 (37.5%)	32
Total	30	24	54

Table 4. Mean TBUT in Travoprost Group

Chi-square value: 8.47; p-value: 0.0036

Schirmer Test Result (mm)	Latanoprost Group (with BAK)	Travoprost Group (without BAK)	Control Group
≤2	0 (0.0%)	0 (0.0%)	0 (0.0%)
3 to 5	0 (0.0%)	0 (0.0%)	0 (0.0%)
6 to 10	2 (8.3%)	0 (0.0%)	0 (0.0%)
>10	22 (91.7%)	24 (100.0%)	30 (100.0%)
Total	24 (100%)	24 (100%)	30 (100%)

Table 5. Schirmer's Test Result in Travoprost Group and Latanoprost Group

A normal TBUT was found in 76.7% of the controls while 79.2% of the patients in latanoprost group had TBUT between 6 and 10 seconds and 8.3% of the latanoprost group had TBUT 5 seconds. The intergroup difference between latanoprost group and control group was statistically significant (p<0.0001). None of the subjects in control and travoprost group had TBUT of 5 seconds or less. 62.5% patients in travoprost group had TBUT between 6 and 10 seconds while 76.7% of the controls had normal TBUT. The intergroup difference was statistically significant (p=0.0036). As regards Schirmer test results, all patients in the travoprost group and all the controls had Schirmer test result >10 mm while 91.7% of the patients in latanoprost group had Schirmer test result >10 mm. The intergroup difference was not statistically significant (p=0.14) All the patients in travoprost group and control group had scored >10 mm and hence were not compared.

DISCUSSION

We had divided our patients and controls based on Tear Break Up Time (TBUT) as per the classification scheme given by International Dry Eye Workshop (DEWS) into three subgroups: - those with TBUT ≤5 seconds (suggestive of having severe dry eye), those with TBUT 6 to 10 seconds (suggestive of having moderate dry eye) and those with TBUT >10 seconds (suggestive of normal tear film stability). We could observe 2 cases in BAK-preserved latanoprost group only with TBUT ≤5 seconds. Overall Latanoprost group had the maximum number of eyes (79.2%) with TBUT between 6 and 10 seconds suggestive of tear film instability. In preservative-free travoprost group, 62.5% of the eyes had TBUT between 6 and 10 seconds.

In a prospective study by Aihara et al. it was seen that switching from BAK preserved latanoprost to SofZia preserved travoprost after 3 months of therapy with the former significantly increased the TBUT (0.1 ± 2.5 to 0.9 ± 2.9 seconds) while there was no significant change in TBUT (0.0 ± 1.5 to 0.1 ± 1.8 seconds) in those subjects who continued with BAK preserved latanoprost.[9] In another study from Croatia, TBUT has been reported to be significantly lower from baseline after 3 months of treatment with BAK preserved travoprost (11.70 ± 1.86 seconds versus 8.30 ± 1.29 seconds; p<0.001).[7]

In the RCT reported by Baudouin and Lunardo, TBUT was significantly reduced from baseline by preserved carteolol at 3 hours (10.4 seconds to 6.1 seconds, p=0.001), whereas benzalkonium free carteolol did not change the TBUT significantly (baseline 9.1 seconds to 7.9 seconds, not significant). The decrease of TBUT from baseline was significantly higher in the benzalkonium group. In the same study, after 6 instillations for 3 days, the TBUT was reported to decrease significantly from baseline (10.4 seconds to 7.7 seconds; p=0.04) in the benzalkonium group while in the benzalkonium-free group the decrease was insignificant (9.1 seconds to 8.4 seconds).[10]

On the contrary, Crichton et al. have reported no significant change in TBUT from baseline, nor any significant decrease in TBUT at the end of 12 weeks of therapy following switching from BAK-preserved latanoprost to either of the three; - BAK-preserved bimatoprost, SofZia preserved travoprost or BAK-preserved latanoprost in three groups of patients.[11] However, it must be noted that the baseline recorded TBUT in these patients were 9.7 seconds, 9.7 seconds and 9.3 seconds (all of them <10 seconds) in the above mentioned three groups respectively. Secondly most patients had received treatment for glaucoma at the time of enrolment in the study with as many as 50% patients having received treatment for ≥3 years. Patients with dry eye disease were not excluded from the study. Thus it is speculative that most patients possibly had a lower TBUT at the time of enrolment in the study owing to treatment with BAK-preserved formulation beforehand. It must also be remembered that two of the groups had received BAK-preserved formulations after the switch, which also explains the absence of any significant change in TBUT. Keeping these facts in light this study only consolidates the fact that BAK preserved formulations do cause the TBUT to be affected detrimentally. Uusitalo et al. enrolled patients who had developed ocular signs and symptoms of ocular surface

disease during treatment with BAK-preserved latanoprost eye drops (containing 0.02% Benzalkonium Chloride). They were switched to preservative-free tafluprost and were evaluated for 12 weeks. The TBUT reportedly improved significantly from 4.5 ± 2.5 seconds at baseline to 7.8 ± 4.9 seconds at week 12 ($p<0.001$).[11]

Keeping the above facts in mind, one can conjecture the hypothesis that BAK-preserved latanoprost had a greater detrimental impact on tear film stability when instilled on a long term basis. The available literature supports this hypothesis. Most of the available literatures[9-11] have described the immediate effect and short term effect of BAK-preserved formulations on TBUT. Our study extrapolates the same facts for long term. In our study Schirmer test was not significantly different between the groups ($p=0.09$). Uusitalo et al. enrolled patients who had developed ocular signs and symptoms of ocular surface disease during treatment with BAK-preserved latanoprost eye drops (containing 0.02% Benzalkonium Chloride) and then they were switched to preservative-free tafluprost and were evaluated for 12 weeks. Schirmer test scores had improved and were statistically significant at 6 weeks but not at 12 weeks. The percentage of patients with abnormal Schirmer test at baseline had improved from 71.5% to 61.5% at 6 weeks and 59.4% at 12 weeks. Our study was a long term study and similar to the study of Uusitalo et al. the changes in Schirmer test results after 1 year of instillation of the drugs were not significant.[12] This finding makes sense because Schirmer test is a reflection of the secretory function of the tear system and is dependent on neural and environmental inputs and thus is unlikely to be affected by topical medications.

CONCLUSIONS

In this study, long term instillation of preservative-free travoprost and BAK-preserved latanoprost was significantly associated with a diminished tear break up time (TBUT) with majority of the patients instilling the drops had a TBUT between 6 and 10 seconds which is consistent with moderate dry eye disease. This effect was strongest in patients instilling BAK-preserved latanoprost. Schirmer test results showed no significant change in between the groups. A conclusion can be made that long term instillation of prostaglandin analogues can be associated with tear film instability. BAK-preserved drugs may have a greater deleterious effect on the tear film than preservative-free drugs. Hence, considering the fact that glaucoma patients need to instill their medications life-long, it might be prudent to choose a preservative-free formulation for such patients.

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