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Original Research Article

EVALUATION OF DRY EYE DISEASE IN PATIENTS OF PRIMARY OPEN ANGLE GLAUCOMA UNDER TOPICAL TIMOLOL MALEATE

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Abstract

Objective: To evaluate the effects of topical Timolol maleate (0.5%) eye drops on the tear film for assessment of dry eye disease (DED) on Primary Open Angle Glaucoma (POAG) patients. **Materials and Methods:** It was an institution based prospective comparative study of 50 patients. Among them, 25 patients diagnosed with bilateral POAG under treatment with topical timolol maleate (0.5%) constituted the "Case group". The "Control group" consisted of 25 patients attending the OPD who came only for refraction test, matched for age and gender with the case group. The assessment for dry eye disease (DED) was conducted by using of Schirmer's test-1 and Tear film break uptime test (TBUT). **Results:** In "Case/Timolol Group", there were 16 male and 9 female patients. And "Control group", there were 17 males and 8 females. The mean age of Timolol group was 54.28±2.59 years and 54.4±2.84 years was Control group. Schirmer's test-1, at the end of 8 month result for the right eye was 16.8 ±1.43 and 16.8 ±1.43 mm in Timolol group and Control group respectively. The p-value was <0.0001*and it was statistically highly significant. And also, in left eye Timolol group and Control group at the end of 8 month was 14.2±1.89 and 16.88±1.27 mm. It was statistically highly significant. TBUT Test, at the end of 8month right eye was 13.32±2.04 and 16.08±1.66, and left eye was 13.32±1.91 and 16.08±1.68 Timolol and Control group respectively. In both eyes (right and left) TBUT Test was highly statistically significant at the end of study. **Conclusion:** In POAG, topical beta blockers like timolol reduce intra ocular pressure by lowering aqueous humour production. However, continuous long term use damages the tear film mucin layer, lowering tear production and reflex tear secretion by diminishing corneal sensitivity. These reduces Schirmer's test-1 values and also TBUT, causing DED.

INTRODUCTION

Primary Open Angle Glaucoma (POAG) is a chronic progressive optic neuropathy characterized by gradual visual field loss and optic nerve damage, often leading to irreversible blindness if left untreated. Timolol maleate, a non-selective beta-adrenergic receptor blocker, has been a mainstay in the management of POAG due to its efficacy in lowering intraocular pressure (IOP) and reducing the progression of the disease. However, the use of topical timolol maleate has been associated with ocular surface adverse effects, notably dry eye disease (DED)[1].

DED is a multifactorial condition characterized by ocular discomfort, visual disturbances, and tear film instability, which may result in damage to the ocular surface. The relationship between topical antiglaucoma medications, particularly timolol maleate, and the development or exacerbation of dry eye symptoms has gained significant attention in recent years[2].

Several studies have reported an association between the use of topical antiglaucoma medications, including timolol maleate, and the prevalence of DED. The mechanisms behind the development of DED in patients receiving timolol maleate therapy are multifaceted, including decreased tear production, altered tear film dynamics, and ocular surface inflammation[3].

The evaluation of DED in patients with POAG under topical timolol maleate therapy is of paramount importance to understand the extent of ocular surface complications and to optimize management strategies[4]. However, limited studies have specifically investigated the relationship between POAG patients receiving timolol maleate and the incidence and severity of DED.

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This study aims to address this gap by evaluating the occurrence and severity of DEDin patients diagnosed with POAG receiving topical timolol maleate compared to age and gender-matched controls.

MATERIALS AND METHODS

Study Centre: Out Patient Department (OPD) and Glaucoma clinic at Midnapore Medical College.
Study Population: Patients attending at OPD.
Study Period:12 months (1st January, 2022 – 31st December 2022). Cases and controls were selected over the period of first 4 months and data were collected over the period of next 8 months.
Sample Size:100 eyes 0f 50 patients attending OPD and Glaucoma clinic were included in this study. 25 of them with diagnosis of bilateral POAG receiving topical timolol maleate (0.5%) were considered as cases. The other 25 patients came for only refraction such as refractive error, early immature cataract, presbyopia matched with the age and gender category with the cases were considered as control. Patients were enrolled in the study after they had given written consent and considered suitable as per inclusion/exclusion criteria. Approval from the institutional ethics committee was obtained prior to the onset of the study.
Inclusion Criteria

- Freshly diagnosed Patient as POAG with mean IOP range from 24-36mmHg.
- Patient of 40 years and above age group.
- Patient willing to give informed consent.
- Cases and controls will be taken with age and gender matched.

Exclusion Criteria

- Severe ocular trauma at any time, previous history of intraocular surgery or argon laser trabeculoplasty, current use of contact lenses, presence of eyelid or eyelash deformity.
- History of recent ocular inflammation or infection.
- Previous or current use of other ocular medications including artificial tear therapy, systemic treatment known to affect tear secretion.
- One eyed persons, autoimmune disease, and ocular surface disorders patients.

Study Design
Institution based prospective placebo-controlled comparative study.
Tests used in This Study
Schirmer test-1: The Schirmer's test is a useful assessment of aqueous tear production. The test involves measuring the amount of wetting of a special (no. 41 Whatman) filter paper, 5 mm wide and 35 mm long. The filter paper is folded 5 mm from one end and inserted at the junction of the middle and outer third of the lower lid, taking care not to touch the cornea or lashes. The patient is asked to keep the eyes gently closed. After 5 minutes the filter paper is removed and the amount of wetting from the fold measured. Less than 10 mm of wetting after 5 minutes without anaesthesia or less than 6 mm with anaesthesia is considered abnormal. Results can be variable and a single Schirmer test result should not be used as the sole criterion for diagnosis of DED, but repeatedly abnormal tests are highly supportive.
Tear film break-up time: The tear film break-up time (TBUT) is abnormal in aqueous tear deficiency and meibomian gland disorders. Fluorescein 2% or an impregnated fluorescein strip moistened with non-preserved saline is instilled into the lower fornix. The break up time (BUT) is the interval between the last blink and the appearance of the first randomly distributed dry spot. A BUT of less than 10 seconds is suspicious. The development of dry spots always in the same location may indicate a local corneal surface abnormality (e.g. epithelial/ basement membrane disease) rather than an intrinsic instability of the tear film.
Study visits and data collection: All the study subjects i.e. cases and controls were recruited at baseline visit after measuring all the parameters. After baseline visit the study subjects were followed up regularly and end of the study visit happened 8 months after the baseline visit with measuring the study parameters again. The results of the Schirmer test-1 and TBUT test were compared between the groups at baseline and at the end of the study. In between the intra ocular pressure, optic disc changes if any were checked and also automated perimetry was done when needed.
Statistical Analysis: In this study the analysis of the data has been done using Mann-Whitney's U test to compare the results of Schirmer's test and TBUT test between the cases and controls. $P<0.05$ was considered statistically significant. Microsoft Excel has also been used to analyze data for interpretation and preparation of tables.

RESULTS

This present study was conducted with100 eyes of 50 patients considering both eyes. All the parameters were checked at the beginning of the study and at every follow-ups. Data recorded of Schirmer's test-1 and TBUT at first visit and at 8months visit. Results of the Schirmer's test-1 and TBUT were expressed as mean ± standard deviation and compared using Mann-Whitney u test.
In "Timolol/Case" group, there were 16 male patients and 9 female patients. In the "Control" group, there were 17 male patients and 8 female patients. Not significant, determined by Fischer's exact test p value was 1.00. [Table 1]
The mean age of patients receiving topical timolol for POAG was 54.28±2.59 years. In the control group, not receiving timolol for glaucoma but matched for age and gender, had a mean age of 54.4±2.84 years. The calculated p-value between the two groups based on age distribution was 0.8767*. This p-value suggests that there was no statistically significant

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difference in the mean ages between the Timolol group and the Control group. [Table 2]

In Timolol group mean Schirmer's test-1 result for the right eye at the beginning of the study was 17.64 ±1.68 mm. In the Control group, the mean Schirmer's test-1 result for the right eye at baseline was 17.8±1.71 mm. The p-value at baseline was 0.70, suggesting no statistically significant difference in the two groups initially. At the end of 8 months, in Timolol Group the mean Schirmer's test-1 result for the right eye decreased to 14.2±1.98 mm. Conversely, in the Control group at 8 months, the mean Schirmer's test-1 result for the right eye was 16.8 ±1.43 mm. The p-value comparing the Schirmer's test-1 results between the Timolol and Control groups after 8 months was <0.0001*. It was statistically highly significant. [Table 3]

The p-value comparing the Schirmer's test-1 results of left eye between the Timolol and Control groups after 8 months was <0.0001*. That was statistically highly significant. [Table 4]

The p-value comparing the TBUT test results between the Timolol and Control groups after 8 months was <0.0001*, indicating statistically highly significant. [Table 5]

The p-value comparing the TBUT test results between the Timolol and Control groups after 8 months was <0.0001*. That was statistically highly significant. [Table 6]

Table 1: Gender distribution of both groups

Gender	Timolol	Control	P value
Male	16	17	1.00*
Female	9	8	
Total	25	25	

Table 2: Age distribution of both groups

Timolol	Control	P value
54.28±2.59	54.4±2.84	0.8767*

Table 3: Schirmer's test – 1 result on right eye of both the groups

	Timolol	Control	P value
Baseline	17.64±1.68	17.8±1.71	0.70
End of 8 months	14.2±1.98	16.8±1.43	<0.0001*

Table 4: Schirmer's test-1results on left eye of both the groups

	Timolol	Control	P value
Baseline	17.68±1.67	17.96±1.59	0.57
End of 8 months	14.2±1.89	16.88±1.27	<0.0001*

Table 5: TBUT test results on right eye of both the groups

	Timolol	Control	P value
Baseline	17±1.53	16.9±1.68	0.72
End of 8 months	13.32±2.04	16.08±1.66	<0.0001*

Table 6: TBUT test results on left eye of both the groups

	Timolol	Control	P value
Baseline	17±1.44	17±1.69	0.73
End of 8 months	13.32±1.91	16.08±1.68	<0.0001*

DISCUSSION

In our study ,100 eyes of 50 patients were examined. The patients were divided in 2 groups – Timolol group containing cases of freshly diagnosed bilateral POAG and control group containing patients who came only for refraction test (i.e. presbyopia, early immature cataract) not receiving any eye drops. Both the groups were matched regarding to age and gender.

In Timolol Group, there were 16 males and 9 females and in Control group, 17 males and 8 females.64% are male and 36% of the patients are female. The mean age of Timolol group was 54.28±2.59 years and Control group was 54.4±2.84 years.

The purpose of the study was to evaluate the occurrence of DED due to topical anti glaucoma drug Timolol maleate (0.5%) eye drops in patients with bilateral POAG. Schirmer's 1 test was done to compare deficiency of aqueous tear production between cases and controls for assessment of DED. and TBUT test for evaporative dry eye disease.

Mean Schirmer's 1 values of right eye in timolol group were 17.64±1.68 and 14.2±1.98 at baseline and at the end of 8 months respectively. The same for the control group were17.8±1.71&16.8±1.43. Similarly in the left eye Schirmer's 1 test mean values were 17.68±1.67 &14.2±1.89 at baseline and at the end of 8 months in Timolol group respectively. The same values were 17.96±1.59&16.88±1.27 in Control group. Though the values were similar at baseline, the values after at the end of 8 months has clearly shown significantly decrease in Timolol group compared to the control group. The results of TBUT test for right eye in timolol group were

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17±1.53&13.32±2.04 at baseline and at the end of 8 months respectively. The same values in control group were 16.9±1.68 and 16.08±1.66 respectively. The results of TBUT test for left eye in timolol group were 17±1.44&13.32±1.91 at baseline and at the end of 8 months respectively. The same values in control group were 17±1.69 &16.08±1.68 respectively. Though the values were similar at baseline, the values after at the end of 8 months has clearly shown significant decrease in Timolol group compared to the control group. This study clearly shows that use of timolol might cause DED if used in long time.

Arici et al,[5] observed a statistically significant decrease in the number of patients with normal Schirmer's test values after timolol administration for three years. Donocik et al,[6] in their study of influence of betaadrenergic antagonist on tear secretion have observed significant decrease in Schirmer's test values in children treated with timolol twice daily for 12 months. Kuppens et al,[7] have studied basal tear turnover rate using flurophotometry in patients who have used timolol 0.5% (with and without the preservative benzalkonium chloride) for a mean duration of 3.5 years and observed that the basal tear turnover rate is slightly decreased in timolol with benzalkonium chloride group as compared to controls and the group administered with timolol without benzalkonium chloride.

Yalvic et al[8] and Levi et al[9] had reported significant decrease in Schirmer's test values. This significant decrease is due to decreased tear production from lacrimal gland and inhibition of reflex tears secretion due to local anaesthetic effect on cornea. The decrease in tear break up time indicate instability of precorneal tear film, which could be due to benzalkonium chloride, used as a preservative in drugs used in present study. Benzalkonium chloride is inserted into lipid monolayer of tear film and disrupts it by detergent action.

Tear film, normally needs to be stable during the inter blink interval. When the tear film is compromised by deficiency of one of the compositional factors, there is an increase in the rate of blinking as a compensatory mechanism to reduce the tear evaporation rate.

However, when there is a failure of all the compensatory mechanism to stabilize the tear film, lipid contamination of the mucin layer occurs, leading to rupture of the tear film and a dry spot formation. TBUT is a measure of the length of time the eye can be kept open before the tear film ruptures spontaneously and is used as a measure of the stability of the tear film.

Strempel et al[10] also observed significant decrease in break up time with topical beta blockers which may be due to influence on tear production and composition or a membrane stabilising effect or some unknown factor that leads to break up time alteration.

J. Thygesen et al[11] investigated and compared the short-term effect of latanoprost and timolol eye drops on tears and the ocular surface in patients with POAG and ocular hypertension. Thirty-seven patients were included in this randomized, double-masked, parallel group study. Patients received either latanoprost 0.005% (n=18) or timolol 0.5% (n=19) instilled once daily in the morning for a treatment period of 27 days. Results showed that after one drop of medication, tear secretion was significantly reduced by timolol, but not by latanoprost. At the end of the study the tear break-up time (TBUT) was significantly decreased in the timolol group but not in the latanoprost group. The symptoms on chronic administration like burning and itching, dry sensation, grittiness and erythema are mainly due to altered tear film and DED.

Baudouin et al,[5] observed that benzalkonium chloride which is used as preservative in anti-glaucoma preparations has shown strong evidence of toxicity to ocular surface.

In this study the drugs used benzalkonium chloride (BAK) as preservative. BAK is the most frequently used preservative in ophthalmic solutions today, and its concentration in glaucoma formulations ranges from 0.004 to 0.02%. The reasons for the frequent use of BAK as a preservative includes its extreme efficacy in combating microbial contamination of bottles, its ability to break cell–cell junctions in the corneal epithelium. Adverse effects attributed to BAK, including conjunctival inflammation and fibrosis, tear film instability, corneal cytotoxicity, anterior chamber inflammation, trabecular meshwork cell apoptosis, cataract development, macular edema, and even systemic effects. These effects can lead to ocular discomfort, poor intraocular pressure control, glaucoma surgery failure, and decreased patient compliance.

Therefore either the preservative alone or the drug alone or both together could be responsible for various DED changes observed.

CONCLUSION

At the end of study, we conclude that on long term therapy of topical anti glaucoma drugs, Timolol maleate (0.5%) cause DED in terms of decreased Schirmer's test-1 and decreased TBUT in both the (right and left) eyes of the patients. Topical beta blockers, such as timolol in this study, are commonly recommended as a treatment for POAG. These medications work by inhibiting the formation of aqueous humour, hence lowering intraocular pressure. Nevertheless, with prolonged use, they harm the protective mucin layer of the tear film, reduce the formation of tears, and inhibit the natural reflex tear secretion by diminishing the sensitivity of the cornea. As a result, there is a decrease in Schirmer's test-1 values and a reduction in TBUT. Prolonged use of this medication may cause a progressive decline in Schirmer's test-1 and TBUT test scores, leading to the development of DED.

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