Original Article

Effects Of Long-Term Use of Topical Antiglaucoma Drugs on Ocular Surface: A Cross Sectional Study

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Abstract

Purpose: *Glaucoma is a chronic progressive disease and a major risk factor for blindness. This study aimed to evaluate the long-term effects of topical antiglaucoma drugs on ocular surface.*

Methods: *This was a cross-sectional study, which included patients with glaucoma who had been taking one/two/three topical drugs (minimum 3 months) and control group of newly diagnosed glaucoma (10 months). The patients were divided into test groups A1 (timolol 0.5%/ briminodine 0.1%/ bimatoprost 0.01%), A2 (dual combination of any of the above drugs), A3 (triple combination) and control. Schirmer-I, tear film breakup time (TBUT), rose bengal, conjunctival impression cytology and ocular surface disease index (OSDI) scores were evaluated.*

Results: *A total of 164 patients were enrolled and divided into groups A1, A2, A3 and control, respectively. There was a significant difference in Schirmer's test (mm) results between the groups (15.06, 13.77, 11.24 and 21.26 in A1, A2, A3 and control, respectively; p<0.001). The mean TBUT (seconds) was 9.84, 8.25, 5.29 and 12.33 in A1, A2, A3 in control group, respectively (p<0.001 timolol 0.5% plus briminodine 0.1% plus bimatoprost 0.01%). Abnormal rose bengal was higher in A2 and A3 than A1 (3.94, 5.92 and 2.55, respectively; p<0.001). The mean conjunctival impression cytology grades were more severe in subgroups A1 (1.83), A2 (1.70) and A3 (2.74) than control group (0.96). The mean OSDI scores were significantly (p<0.001) higher in A2 (34.62) and A3 (49.63) than A1 (25.93).*

Conclusion: *Topical antiglaucoma drugs caused OSD on long term use. The severity of OSD was higher in multiple drug combinations in comparison to single drug.*

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Introduction

The patients with primary open-angle glaucoma (POAG) have a reduced quality-of-life even in milder cases and during initial stages of the disease that worsen with time.[7] The management include surgical/pharmacological approach with systemic/topical agents in combination of two/three drugs belonging to different classes with the primary target of lowering intraocular pressure(IOP).[10-12] The most commonly used antiglaucoma drugs are prostaglandins prescribed as once-daily dose (latanoprost, travoprost, bimatoprost), β-blockers (timolol), and α-agonist as twice-daily dose (brimonidine).

Despite proven efficacy timolol, brimonidine and bimatoprost, these drugs have ocular and systemic adverse effects.[13,14] Prostaglandin analogues are potent and first line IOP lowering drugs used in POAG.[15] However, bimatoprost is reported to cause conjunctival hyperemia.[16-18] Timolol is reported to cause a significant reduction in tear production and adversely affects corneal sensitivity and ocular surface.[19] Brimonidine also has good safety and tolerability but higher incidence of conjunctival hyperemia and allergic conjunctivitis.[20-22] Considering the unfavorable effects with current glaucoma medications, patient compliance and tolerability are affected adversely due to which newer molecules and drug delivery systems are being researched.[23]

In this study, the long-term effects of topical timolol 0.5%, brimonidine 0.1%, bimatoprost 0.01% on the ocular surface and tear film were investigated. Further the effect of monotherapy vs. dual and triple therapies in patients with glaucoma on ocular surface was evaluated. Since limited Indian studies are reported in literature comparing the effect of monotherapy vs. dual and triple anti-glaucoma therapies comprising of timolol, brimonidine and bimatoprost on the ocular surface in POAG, the outcomes of this study would be an add on data for clinician's reference as well as to the already established evidence.

Materials and Methods

This was a cross-sectional study conducted at the Department of Ophthalmology, Sahai Hospital and Research Centre, Jaipur, Rajasthan from January to October 2019. The study was approved by Institutional Ethics Committee (NHMECJ/JPR/2019/01). Written informed consent was obtained from all the study patients before enrolment.

Patients with POAG who had been taking one/two/three topical antiglaucoma drugs for a minimum of 3 months and who were newly diagnosed with POAG in past 10 months (with no past history of topical antiglaucoma medications) were included in this study. The exclusion criteria were, all other forms of glaucoma like primary angle-closure glaucoma (PACG), secondary glaucoma, presence of active ocular inflammation or allergy, any ocular pathology which can disrupt ocular surface (entropion, ectropion, pterygium, concretions, chalazion), ocular trauma, symptoms and any treatment of prior dry eye (punctual plugs, topical corticosteroids), patients with history of previous glaucoma surgery, any surface refractive surgery, contact lens wearers, systemic diseases (asthma and cardiac disease), diabetes mellitus, and autoimmune diseases.

The patients were divided into test (patients on topical antiglaucoma drugs) and control group. Test group were subdivided into A1: patients on single antiglaucoma drug

either timolol 0.5%, brimonidine 0.1%, or bimatoprost 0.01%; A2: patients on dual combination of any of the two antiglaucoma drugs mentioned in A1 group; and A3: patients on triple antiglaucoma drug combinations mentioned in A1 group. The groups A2 and A3 were prescribed with drug combinations rather than multiple separate drug preparations. The control group included patients with newly diagnosed of POAG (with no past history of topical antiglaucoma medications).

Patient examination was conducted for visual acuity (on Snellen's chart), best corrected visual acuity, slit lamp examination, applanation tonometry to measure IOP, gonioscopy with Goldman single mirror lens, fundus examination with +90D lens slit lamp biomicroscopy, Humphrey visual 30-2 for tear break-up time test (TBUT), rose bengal staining of ocular surface, conjunctival impression cytology, Schirmer's -I test and ocular surface disease index (OSDI) questionnaire study.

The Schirmer-1 test was performed without anesthesia by placing a standardized strip of filter paper (Whatman filter paper no.41) in the one-third lateral tarsal conjunctiva away from the cornea. The TBUT test was performed by applying fluorescein solution onto the inferior palpebral conjunctiva after gentle depression of the lower eyelid. A clinically abnormal TBUT was defined as less than or equal to 10 seconds.[24] Rose bengal (1%, 2μL) was instilled into the conjunctival sac. The dye stained all eroded and denuded areas of the corneal and conjunctival epithelial cells.[25]

In conjunctival impression cytology of the ocular surface, a 25 mm diameter nitrocellulose membrane filter (filter type 0.22 μm; GSWP, Merck Millipore, Billerica, MA, USA) was cut into half and trimmed into strips of approximately 4×6 mm. After instillation of one to two drops of topical anesthetic (Alcaine; Alcon, Puurs, Belgium) and wiping away the excessive tear fluid, the strip of filter paper was gently pressed on the conjunctiva with a glass rod. After 5-10 seconds, the filter paper was peeled off and the cells were transferred by imprinting onto poly-L-lysine-coated glass slides. Specimens were collected from the inferior and temporal bulbar conjunctiva of the selected study.[26] The slides were air-dried and stained with hematoxylin and eosin stain. Specimens were analyzed by light microscopy using modified Nelson's grading scheme (grades 0-3) based on the appearance of epithelial cells and the density of goblet cells.[27] Grades 0 and 1 are present in normal conjunctiva with nucleus-to-cytoplasm (n/c) ratio up to 1:3, whereas grades 2 and 3 are abnormal (n/c ratio >1:4) and indicate squamous metaplastic changes seen in many inflammatory conditions (dry eye, use of antiglaucoma therapy, contact lens wearers). All the patients completed OSDI which is a 12-item questionnaire designed to provide a rapid assessment of the symptoms of ocular irritation consistent with dry eye disease and their effect on vision related functioning.[28]

Statistical analysis

Categorical variables were presented as proportions and compared using Pearson's Chi-square test. Continuous variables were presented as mean (standard deviation) or median and range and compared using Student's t-test or Mann-Whitney U test (for comparison between test and control group), depending upon distribution of the data. Comparison of continuous variables between three or more groups (i.e. Group A1, A2, and A3) was made using one-way ANOVA or Kruskal-Wallis test depending upon the distribution of data. If a statistically significant difference was found ($p<0.05$), a post-hoc multiple comparison procedure (Tukey test) was used to compare each group. Statistical analyses were performed using the Statistical Package for Social Sciences version 20.0 (IBM Corp, Armonk, NY).

Results

A total of 164 patients were enrolled in this study, of these, 109 patients were included in the test group (A) while 55 patients were included in control group. Test group was further subdivided as A1, A2, and A3, according to the number of antiglaucoma drugs being used. The demographics of the subjects are summarized in (Table 1). Ocular surface disease was evaluated according to the number of eyes that is 218 cases and 110 control, considering that two eyes have different base line IOP and slightly different morphology.

There was a significant difference in mean Schirmer's test results between the groups ($p<0.001$). The mean Schirmer's test (mm) was 15.06, 13.77, 11.24, and 21.26 in A1, A2, A3 and control group, respectively. The mean of TBUT (seconds) was 9.84, 8.25, 5.29 and 12.33 in A1, A2, A3 and control group, respectively. The mean rose bengal was more common in A3 (5.92) followed by A2 (3.94), A1 (2.55) and control group (1.21). The subgroup differences were statistically significant ($p<0.001$). There was a significant difference between the mean conjunctival impression cytology grades of subgroups A3 (2.74), followed by A1 (1.83) and A2 (1.70) compared to control group (0.96; $p<0.001$) (Table 2). The mean OSDI scores were significantly high in subgroups A2 (34.62) and A3 (49.63) compared to A1 (25.93) ($p<0.001$). Ocular surface disease increases with the increase in the duration of medications (A1 [5.10], A2 [6.62], and A3 [13.16] months; $p<0.001$) (Table 2).

Table 1: Patient demographics

Parameters	Test			Control (n=55)
	A1 (n=40)	A2 (n=50)	A3 (n=19)	
Age, mean (SD)	51.88 (10.40)	53.20 (9.02)	55.00 (9.82)	54.44 (8.69)
Sex Men	17 (42.50)	28 (56.00)	8 (42.11)	23 (41.82)
SexWomen	23 (57.50)	22 (44.00)	11 (57.89)	32 (58.18)
Data shown as n (%), unless otherwise specified. SD, standard deviation.				

The number of eyes in the test group who had abnormal Schirmer's tests was significantly more than control group (59.17% vs. 4.55%, $p<0.001$). The percentage of prevalence with abnormal TBUT (seconds), rose bengal (grade) staining and impression cytology was significantly more common in the test group (66.06%, 63.30%, and 72.48%, respectively) compared to control group ($p<0.001$). The OSDI score was also significantly higher in test group (63.76% vs. 9.09%; $p<0.001$) (Table 3). The number of eyes with abnormal OSD tests were significantly high in test group compared to the control group ($p<0.001$) (Table 4).

Table 2: Summary of results

Parameters	Test			Control (n=110)	P value
	A1 (n=80)	A2 (n=100)	A3 (n=38)		
Schirmer's test (mm)	15.06 (3.18)	13.77 (3.11)	11.24 (4.38)	21.26 (4.01)	<0.001
TBUT (s)	9.84 (2.05)	8.25 (2.31)	5.29 (1.83)	12.33 (2.20)	<0.001
Rose bengal (grade)	2.55 (1.33)	3.94 (1.86)	5.92 (1.92)	1.21 (0.46)	<0.001
Impression cytology	1.83 (0.82)	1.70 (0.70)	2.74 (0.45)	0.96 (0.60)	<0.001
OSDI score	25.93 (7.69) [n=40]	34.62 (10.86) [n=50]	49.63 (5.12) [n=19]	19.93 (5.38) [n=55]	<0.001
Duration of drugs (months)	5.10 (1.69) [n=40]	6.62 (2.47) [n=50]	13.16 (3.95) [n=19]	-	<0.001

Data shown as mean (SD).
n= Total number of eyes
mm, millimeter; OSDI, ocular surface disease index; SD, standard deviation; TBUT, tear film breakup time.

Table 3: Prevalence of OSD in patients on antiglaucoma drugs

Parameters	Test (n=218)	Control (n=110)	P value
Schirmer's test (mm)	129 (59.17)	5 (4.55)	<0.001
TBUT (s)	144 (66.06)	6 (5.45)	<0.001
Rose bengal (grade)	138 (63.30)	2 (1.82)	<0.001
Impression cytology	158 (72.48)	14 (12.73)	<0.001
OSDI score	139 (63.79)	10 (9.09)	<0.001

Data shown as n (%).
n= Total number of eyes
OSDI, ocular surface disease index; TBUT, tear film breakup time.

Table 4: Number of positive OSD test in test and control eyes

Tests	Test (n=218)	Control (n=110)	P value
0	20 (9.17)	94 (85.45)	<0.001
1	42 (19.27)	6 (5.45)	
2	16 (7.34)	4 (3.64)	
3	12 (5.50)	3 (2.73)	
4	42 (19.27)	1 (0.91)	
5	86 (39.45)	2 (1.82)	

Data shown as n (%). OSD, ocular surface disease.
The OSD tests include Schirmer's test, tear film break up time (TBUT), Rose Bengal, Impression cytology, and ocular surface disease index (OSDI) score.

Discussion

Various experimental and clinical studies have shown that the use of topical antiglaucoma drugs and preservatives present induce mild to severe discomfort due to ocular surface changes. Hyperemia, conjunctival inflammation and fibrosis, dry eye syndrome, eyelid dermatitis, tear film instability and impaired cornea occur commonly.[29-31] Therefore, considering these factors, the marketed drug formulations which contain same preservatives have been used in this study.

The major findings in this study reveal that chronic use of commercial preparations of timolol, brimonidine and bimatoprost are associated with conjunctival changes leading to damaged ocular surface. Patients enrolled in this study used single as well as dual and triple combination therapies. The severity of OSD was higher in combination drugs than a single drug. Patients with POAG showed associated OSD with abnormal tear production and quality that is in accordance with the reported Indian and global studies.[28,32,33] Previously reported clinical studies report that long-term usage of topical anti-glaucoma drugs adversely affect the ocular surface.[13,34,35] Studies show that the conjunctival surface and tear film function is damaged due to long term use of timolol, brimonidine and bimatoprost as well as with other combinations of beta-blocker, alpha adrenergic agonist, and prostaglandin analogue. However, there is a paucity in studies reporting the effect of timolol, brimonidine and bimatoprost monotherapy and their fixed drug combinations on ocular surface; hence this study was undertaken to determine the comparative effect of long-term usage of these drugs.

Although men are more prone to POAG [36,36], the present study showed women predominance who were in their mid-fifties and this concurs with previously reported studies.[33,38] The ocular surface changes evaluated using Schirmer's test, TBUT, rose bengal staining and impression cytology showed higher abnormality in the test group than the control group.

Investigations reveal that preserved eye formulations cause eye irritation symptoms and adverse effects more than those without preservative.[39] Benzalkonium chloride is the most commonly used preservative in the topical antiglaucoma formulations. Studies report cytotoxicity and proinflammatory effects on the ocular surface, squamous metaplasia of conjunctiva and decrease in the goblet cell number.[40-42] The recently introduced polyquaternium preservative is observed to increase cell death and production of proinflammatory cytokines in human corneal epithelial cell culture.[43]

A prospective epidemiological survey conducted in a series of 4107 patients, studied the ocular toxicity of preservatives present in glaucoma medications. The study demonstrated that 84% patients used preserved eye drops that showed more prevalent but reversible adverse reactions induced by these medications compared to preservative free medication.[41]

The mean Schirmer's test results showed a significant low value in the antiglaucoma subgroups when compared to that of control group. These results are in line with the results of previously reported studies.[43] Saini M et al. conducted a prospective comparative study of ocular surface evaluation on 50 eyes using antiglaucoma medications vs. 50 normal eyes that showed a significantly low mean Schirmer's test score in antiglaucoma eyes than the normal eyes (7.63 [2.64] vs. 12.86 [1.93]; p<0.001).[33]

In the present study, the mean TBUT reported a significantly less time in glaucoma treated subgroups compared to the control group. Also, the mean TBUT in all the subgroups was less than 10 seconds indicating tear instability while the control group reported a mean TBUT of 12.33 seconds indicating a better ocular surface compared to the former. Investigations report a break-up time of <7 seconds (n=79 and n=18) patients with POAG.[26,44] A cross-sectional case comparison study demonstrated that the percentage of abnormal TBUT was rising with the number of topical medications and was significantly higher with both benzalkonium chloride-containing and preservative-free eye drops (90% and 94%, respectively, both p<0.001).[24]

A prospective cross-sectional study in 109 Thai patients receiving topical IOP lowering therapy revealed that rose bengal staining was positive in 39% patients with glaucoma. A number of IOP-lowering eye drops was associated with 4.4 times significantly higher odds of abnormal rose bengal staining (95% CI, 1.91-10.32, p=0.001).[5] Fluorescein staining was also reported by 32% patients which was not performed in the current study. The present study also reported a significantly more abnormal rose bengal staining in A2 and A3 (dual and triple combination) compared to A1 (monotherapy).

This study reported a more severe impression cytology grades in patients treated with antiglaucoma therapy than the control group. The study results were supported by a previous study where the medication group reported a higher impression cytology grades than the control group (median [range]: 1.0 [1:2 to 1:6] vs. 0.6 [1:2 to 1:4]; p<0.001).[26] In this study, monotherapy group reported lower cytology grades than the fixed combination therapy group.

As per the recent study, the mean score of OSDI in groups with eye drops and without eye drops was 11.1 and 9.2, respectively.[26] This study demonstrated significantly higher OSDI scores in A2 and A3 compared to A1. These results are in line with the previous studies reporting ocular disease using OSDI.[5] A study in Spanish patients reported significantly higher median OSDI (10.24 vs. 2.5; p<0.001) in the control group vs. medication group. Another study showed 34% with severe OSDI (Score >32) and 52% patients with at least mild symptoms.[45] Investigations suggest significantly higher total OSDI scores in patients with glaucoma than the normal populations (16.7 vs. 7.9; p<0.001).[28,46] A Malaysian study reported moderate OSDI symptoms (17% vs. 7%, p=0.028) in patients with glaucoma and stated that benzalkonium chloride was related with approximately three times higher odds ratio of having abnormal OSDI.[24]
Furthermore, there was an increasing incidence with higher numbers of eye drops. Each additional eye drop is associated with about two times higher rates of impaired TBUT and attributed this to the preservatives in the eye drops.[47] In this study prevalence of OSD was higher among those on multi-drug therapy compared to monotherapy and it also increased with duration of medication. The common preservative was used in this study, as to exclude the effect of different preservatives on ocular surface.

This study has limitations like the effect of individual antiglaucoma drug on ocular surface was not compared, other types of glaucoma apart from POAG were not included, and sample size. A larger scale prospective study may possibly give a better understanding about the changes in ocular surface during course of disease.

To conclude, this study firmly emphasizes that long term topical antiglaucoma drugs are associated with mild to severe form of OSD. This can occur with multiple drugs or single drug, if used for more than three months, although the degree of severity may vary. Therefore, it is recommended that every patient with POAG visiting the clinic and are administering prolonged topical IOP lowering drugs, should be screened for OSD. Along with antiglaucoma therapy, these patients require management of OSD as well. This will help in reducing the patient's discomfort and will surely improve the compliance of the treatment, which is a very important aspect of glaucoma management.

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