ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 01 | January - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

INCIDENCE OF DRUG RELATED CORNEAL SURFACE CHANGES FOLLOWING LONG TERM USE OF TIMOLOL(0.5%) AND BRIMONIDINE(0.2%)

Ophthalmology

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ABSTRACT

Aim: To study the incidence of drug induced corneal surface changes following long term use of timolol(0.5%) and brimonidine(0.2%). ***Material and Methods:*** In this prospective observational cross-section study 60 eyes of 30 patients with chronic glaucoma using two anti glaucoma drugs for at least 3 months were taken as cases (group A) and 60 eyes of 30 patients without any ocular pathology and not on any anti glaucoma drugs were taken as controls (group B). Every patient was followed up at or after 3 months and detailed ocular examination was conducted which included visual acuity, intra-ocular pressure, schirmer'sI test, corneal surface staining score and tear break time. ***Observation and Result:*** The difference in vision, intra-ocular pressure, schirmer'sI test, tear film breakup time, corneal surface staining score between cases and controls were statistically significant with (paired t-test, P<0.001, P=0.004, P<0.001, P<0.001, P<0.001) respectively. ***Conclusion:*** Combination of Timolol (0.5%) and Brimonidine (0.2%) eye drop with preservative (Benzalkonium chloride, BAC) was used in glaucoma patients and prevalence of ocular surface changes was estimated to be 59%.

KEYWORDS

Intraocular pressure, schirmer'sI test, tear film breakup time, corneal surface staining score.

1. INTRODUCTION

Ocular surface disorders occur due to chronic, long term use of topical anti glaucoma medications. Instillation of topical anti glaucoma drops for a period of three or more months has been found to cause significant subclinical inflammation, which has been detected as increased expression of HLA-DR on conjunctival epithelial cells[1]. Pro-inflammatory cytokine secretion by conjunctival cells has been noted to occur as a result of instillation of topical anti glaucoma eye drops[2-4].

Topical medication related ocular surface disease (OSD) results in major side effects including local allergic reactions, chronic conjunctival inflammation, tear film abnormalities, punctate corneal epitheliopathy, medically resistant herpetic keratitis, disruption of epithelial function, chronic inflammatory infiltration, increased expression of inflammatory markers, impaired wound healing and squamous metaplasia[5-6].

Benzalkonium chloride (BAC, quaternary ammonium compound), the most commonly used preservative in topical antiglaucoma preparations. BAC promotes the activation of lipooxygenases, synthesis and secretion of eicosanoids, inflammatory mediators and many cytokines such as interleukin (IL)-1a, tumor necrosis factor, IL-8, IL-10, resulting in irritation, delayed hypersensitivity and allergic reactions[7].

1.1 AIMS AND OBJECTIVES

To study the incidence of drug induced corneal surface changes following long term use of timolol(0.5%) and brimonidine(0.2%).

2. MATERIAL AND METHODS

A prospective observational cross-sectional study including 60 patients from Outpatient Department of Ophthalmology was conducted at Netaji Subhash Chandra Bose Subharti Medical College, Meerut from December 2018-August 2020. The study included

GROUP A(cases):- 60 eyes of 30 patients with chronic glaucoma using two anti glaucoma drugs for at least 3 months as cases.
GROUP B(controls):- 60 eyes of 30 patients without any ocular pathology and not on any anti glaucoma drugs as controls.

INCLUSION CRITERIA

1. Patients with chronic glaucoma on combination therapy with two topical anti glaucoma medications with preservatives (timolol 0.5% & brimonidine 0.2%) for at least three months.
2. Subjects without any ocular pathology and not on any anti glaucoma drugs as control group.

EXCLUSION CRITERIA

1. Patients who have undergone any previous intraocular surgery.
2. Patients who have undergone any laser treatment in past six months.
3. Contact lens wearers.
4. Patients having any autoimmune disease.
5. Patients with history of any recent ocular infection or inflammation.
6. Patients with history of any recent ocular injection.
7. Eyes with trachoma.
8. Dry eye due to causes other than this.
9. Previous or current use of other ocular medications.

3. Pre-Operative Evaluation

1. Case reporting format.
2. Whatmann no. 41 filter paper strips (5mm x 35mm) for Schirmer's test.
3. Fluorescein stained strips for Tear Film Breakup Time (TBUT) and corneal surface staining score test.
4. Intra-ocular pressure was recorded using non-contact tonometer.
5. Slit lamp biomicroscope for complete ocular evaluation.

STATISTICAL ANALYSIS

Statistical analysis was performed using IBM, SPSS Statistics version 25 (IBM Corp., New York, NY). The test values of continuous variables were expressed as mean ± SD (standard deviation). Dichotomous variables and proportions were compared with Chi-square tests. Continuous variables between cases (anti-glaucoma medication group) and controls (age and sex-matched health subjects) were compared with paired t-tests. A p-value less than 0.05 was considered statistically significant.

4. OBSERVATION AND RESULT

Table 1.- Comparison of IOP in group A & group B

Criteria	Group A		Group B	
	RE	LE	RE	LE
IOP (mmHg)	N (%)	N (%)	N (%)	N (%)
<18	21 (70)	18 (60)	18 (60)	16 (53.3)
18-20	6 (20)	10 (33.3)	12 (40)	13 (43.4)
>20	3 (10)	2 (6.67)	0 (0)	1 (3.3)
Total	30 (100)	30 (100)	30 (100)	30 (100)

The mean intraocular pressure (IOP) in group A was 18.5±1.9 (range, 16-24 mm Hg) and in group B was 17.2±2.84 (range, 12-20 mm Hg), respectively. The difference in IOP was statistically significant (paired t-test, P=0.004).

Table 2.- Comparison of schirmer's I test in group A & group B

Criteria	Group A		Group B	
	RE	LE	RE	LE
SCHIRMER (mm)	N (%)	N (%)	N (%)	N (%)
Severe (<5)	1 (3.3)	0 (0)	0 (0)	0 (0)
Moderate (5-7)	17 (56.7)	20 (66.7)	0 (0)	1 (3.33)
Mild (7-9)	12 (40)	9 (30)	3 (10)	4 (13)
Normal (>10)	0 (0)	1 (3.3)	27 (90)	25 (83.4)
Total	30 (100)	30 (100)	30 (100)	30 (100)

The mean Schirmer test score in group A was 7.2±0.83 (range, 5-10 mm) and in group B was 12±1.36 (range, 11-16 mm), respectively. The difference in Schirmer test score was statistically significant (paired t-test, P<0.001).

Table 3.- Comparison of CFS test in group A & group B

Criteria	Group A		Group B	
	RE	LE	RE	LE
CFS	N (%)	N (%)	N (%)	N (%)
Grade 1 (0-3)	1 (3.3)	4 (13.3)	28 (93.3)	26 (86.7)
Grade 2 (4-8)	28 (93.4)	24 (80)	2 (6.7)	4 (13.3)
Grade 3 (9-14)	1 (3.3)	2 (6.7)	0 (0)	0 (0)
Grade 4 (14-15)	0 (0)	0 (0)	0 (0)	0 (0)
Total	30 (100)	30 (100)	30 (100)	30 (100)

The mean corneal fluorescein score (CFS) in group A was 5.64±1.6 (range, 5-6.6) and in group B was 1.06±0.1 (range, 0.2-4), respectively. The difference in CFS scores was statistically significant (paired t-test, P<0.001).

Table 4.- Comparison of TBUT in group A & group B

Criteria	Group A		Group B	
	RE	LE	RE	LE
TBUT (sec)	N (%)	N (%)	N (%)	N (%)
Low (<5)	1 (3.3)	2 (6.66)	0 (0)	0 (0)
Moderate (5-10)	24 (80)	20 (66.7)	2 (6.7)	4 (13.3)
Mild (>10)	5 (6.7)	8 (26.7)	28 (93.3)	26 (86.7)
Total	30 (100)	30 (100)	30 (100)	30 (100)

The mean tear film break-up time (TBUT) in group A was 8.47±1.31 (range, 5-10 seconds) and in group B was 12.9±1.9 (range, 8-16 seconds), respectively. The difference in TBUT between was statistically significant (paired t-test, P<0.001).

5. DISCUSSION

Ocular surface changes are commonly prevalent in glaucoma patients on topical antiglaucoma medications. The prevalence of ocular surface changes in glaucoma patients on preserved (BAC) containing anti-glaucoma medications has been estimated to be 59%[8]. It is now widely accepted that the frequency of ocular symptoms and signs and ocular irritation are higher in patients treated with preserved than preservative-free eye drops[9]. Preservatives used in topical medications alter epithelial barrier function leading to exposure of corneal nerve endings, irritation, and an unstable tear film resulting in ocular surface epithelial changes[10].

Wong et al[11] conducted a cross-sectional study in thirty-three patients with open angle glaucoma receiving topical anti-glaucoma medication in one eye for at least 6 months were enrolled in the study. The fellow eye served as controls. The test eye had a significantly lower Schirmer test value (P=0.04), non-invasive TBUT(P=0.03), tear film osmolarity (P=0.04), conjunctival hyperaemia (P=0.04) and tear meniscus height than control eyes. On the contrary, in our study, corneal fluorescein staining was significantly lower in test eye as compared to this study. The probable reason for this difference in observation could be attributable to the preservative present in the eye drops. Benzalkonium chloride present in timolol-brimonidine fixed-drug combination is known to cause ocular irritation and long-term anti-glaucoma therapy may cause ocular surface inflammation and ocular surface changes.

Saini et al[12] conducted a prospective study to evaluate ocular surface changes and their correlation with corneal nerve fibre layer in patients with chronic glaucoma. The authors found that OSDI score, Schirmer test score, TBUT, corneal sensitivity and central corneal nerve density were significantly (P<0.001) lower in treatment eyes as compared to controls. The nerve fibre layer density significantly and inversely correlated with corneal staining and positively with TBUT. Although nerve fibre layer density was not evaluated in our study, Schirmer test and TBUT was significantly lower in eyes on anti-glaucoma medications as compared to untreated controls.

6. Limitation

The shortcomings of the present study were a relatively short treatment duration and sample size. Secondly, the study design was not a randomized one adding to selection bias. Although the control group was age and sex-matched, it was not placebo controlled or an active group with preservative-free treatment schedule.

7. CONCLUSION

The following conclusions were made from this study:

1) The mean Schirmer test score in group A was 7.2±0.83 (range, 5-10 mm) and in group B was 12±1.36 (range, 11-16 mm).
2) The mean tear film break-up time (TBUT) in group A was 8.47±1.31 (range, 5-10 seconds) and in group B was 13.3±1.27 (range, 12-16 seconds).
3) The mean corneal fluorescein score (CFS) in group A was 5.64±0.61 (range, 5-6.6) and in group B was 1.04±0.21 (range, 0.6-1.4).

Glaucoma patients on long term fixed drug combination therapy have corneal surface epithelial changes, reduced tear film break up time and reduced Schirmer test values in comparison to controls. The treatment duration may significantly influence these changes in tear film profile and corneal surface.

8. REFERENCES

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