ORIGINAL ARTICLE

Association of Various Topical Antiglaucoma Drugs with Ocular Surface Disorders in Primary Open Angle Glaucoma

Pooja Kanodia [1], Sumit Malhotra [2], Rubie Malhotra[1], Ausaf Ahmad [3] and Akansha Srivastava [1]
[1]Department of Ophthalmology, [3]Department of Community Medicine, Integral Institute of Medical Sciences and Research, Integral University, Lucknow, [2]Department of Surgery, ERAs Lucknow Medical College and Hospital, Lucknow- 226003 , Uttar Pradesh, India.

Abstract:
Background and Objective: Glaucoma is the second leading cause of blindness in the world and is expected to affect 79.6 million people by 2020. Topical medical therapy is the most common treatment for glaucoma, and the patients on topical antiglaucoma treatment are prone to develop ocular surface diseases. The aim of the study was to evaluate the association of various topical antiglaucoma drugs with ocular surface disorders. *Material and Methods:* This prospective, cross-sectional study was conducted at the Department of Ophthalmology, Integral Institute of Medical Sciences and Research, Integral University, Lucknow. A total of 100 eyes of 50 patients of primary open angle glaucoma were enrolled in the study. The study duration was from January 2019 to January 2020. The study subjects were adult patients with diagnosis of primary open angle glaucoma undergoing topical antiglaucoma treatment. Written informed consent was obtained from each participant, which included an explanation of the study design and goals. *Results:* The study comprised 100 eyes of 50 patients of primary open angle glaucoma. Mean age of patients was 57.27 years with 57 % males and 43% females. The patients were divided into six groups. Group 1A and 1B, included patients on Timolol eye drops without and with preservative respectively, Group 2A and 2B, on Brimonidine without and with preservative, Group 3A and 3B, included patients on Travoprost, withoutand with preservative respectively. IOP was decreased significantly in all of the groups at 1st, 3rd, 6th, and 12th months visits compared to baseline. In our study we found an association between the use of antiglaucoma drugs and ocular surface disorder which could be attributed due to the active ingredient or due to presence of preservative in the drug. *Conclusion:* There is an association between the use of antiglaucoma drugs and ocular surface disorders. The ocular surface disorder occurs either due to active ingredient or due to preservative in the drug. OSD in glaucoma patients may be minimised by preferable use of preservative free antiglaucoma drugs.

Keywords: Glaucoma, Medical management, Ocular surface disorders.

Introduction:

Primary open angle glaucoma (POAG) is a progressive neurodegenerative disorder of retinal ganglion cells (RGCs) and their axons characterized by characteristic optic nerve head changes and corresponding visual field defects with or without raised intraocular pressure [1]. There are numerous risk factors for glaucoma, but the major factor that we can treat effectively is intraocular pressure (IOP). The medications used to treat in glaucoma act in two ways, either by decreasing production of aqueous humour or increasing its outflow by conventional or unconventional pathway, thereby reducing IOP. Treatment of glaucoma, frequently includes medical treatment with one or more than one topical anti-glaucoma medication which may cause chronic inflammation or it may aggravate a concomitant ocular surface disease on prolonged use. Ocular surface disorder (OSD) is a multifactorial disorder of the conjunctival and corneal epithelium, lacrimal glands, and meibomian glands of lids that results in either deficient or inappropriate tear production leading to ocular discomfort and decreased visual clarity through various inflammatory pathways [2,3]. The goal of this research was to study the association of different antiglaucoma medications, and ocular surface disorders. Ocular Surface Disorders are prevalent among patients of glaucoma on topical

treatment. There is a higher prevalence of OSD in patients of glaucoma and ocular hypertension as compared to normal population [4]. At present, 11% of the 5 million Americans over 50 who have dry eye disease also have glaucoma [5]. Topical medical therapy is the most common initial treatment for glaucoma, and 49-59% of glaucoma patients on topical anti-glaucomatous medications have ocular surface disease [6]. Topical glaucoma medications can cause burning, irritation, itching, watering, and decrease in visual acuity within three months of medication initiation [7]. The long-term use of topical antiglaucoma drugs may cause ocular discomfort, tear film instability, conjunctival inflammation, subconjunctival fibrosis, corneal surface irregularity, epithelial apoptosis, and the potential risk of failure for further glaucoma surgery with a possible increase in visual loss as shown in experimental and clinical studies [8]. The overall prevalence of Ocular surface disease is 42% (range 20–59%) in glaucoma, with 36% is in severe range (range 14–66%) [9]. The symptoms may include dry eye, burning/stinging, itching, irritation, watering, foreign body sensation, red eye, and blurred vision. The signs may include conjunctival staining, with tear film abnormalities [10]. The ocular side effects may be due to the active component or due to the preservatives or both in the topical medications, but the mechanisms involved and the respective roles of the active compounds and the preservatives in inducing allergic, toxic, or proinflammatory effects of ophthalmic solutions are still under debate [11,12]. Thus, the aim of the study was to evaluate the association of various topical antiglaucoma drugs with ocular surface disorders.

Material and Methods:

This study was a prospective, cross-sectional study conducted at the Department of Ophthalmology, Integral Institute of Medical Sciences and Research, Integral University, Lucknow, Uttar Pradesh, India after gaining approval from Institutional Research and Ethical Committee. The study duration was one year from January 2019 to January 2020. The study subjects included adult patients who presented to the Out patient Department of Ophthalmology, Integral Institute of Medical Sciences and Research, Lucknow, with diagnosis of primary open angle glaucoma undergoing topical antiglaucoma treatment. Written informed consent was obtained from each participant, which included an explanation of the study design and goals. The study included 100 eyes of 50 patients with the diagnosis of primary open angle glaucoma, using topical antiglaucoma drugs of different classes in both the eyes.

A total of 100 eyes of 50 patients of Primary open angle glaucoma were enrolled in the study. The division of patients were done in to six groups, as follows:

Groups	A (without preservative)	B (with preservative)
Group 1	0.5% preservative-free timolol maleate twice a day.	0.5% timolol maleate including preservative 0.015% BAK, twice a day.
Group 2	0.1% brimonidine preservative free twice a day.	0.1% brimonidine including preservative purite 0.005% twice a day.
Group 3	0.004 % travoprost preservative free once a day at night.	0.004% travoprost with 0.015% BAK once a day at night.

All cases of POAG, using topical antiglaucoma treatment were included in the study. (Glaucoma would be defined as intraocular pressure (IOP) more than 21 mmHg on applanation tonometry without treatment, abnormal automatic full threshold perimetry (30/2 Humphrey), and abnormal optic disc (increased cup to disc ratio, cup to disc asymmetry between the two eyes more than 0.2, with or without peripapillary splinter haemorrhages) were included in the study.

Patients with history of recent ocular inflammation or infection, Previous history of argon laser trabeculoplastyor intraocular surgery, Severe ocular trauma at any time, Current use of contact lenses Presence of eyelid or eyelash deformity, Presence of eyelid or eyelash deformity, Previous or concurrent use of other ocular medications including artificial tear

therapy, Systemic treatment known to affect tear secretion and Autoimmune disorders were excluded from the study.

Patient work up includes detailed history related to glaucoma duration and treatment, and history in relation to ocular surface disorders. The general data including age, gender, time since glaucoma diagnosis, class of drug used, previous ocular surgeries and ocular and systemic comorbidities was recorded, followed by a detailed ocular examination. The ophthalmic examination includes best corrected visual acuity, measurement of IOP by applanation tonometry, detailed dilated fundus examination, visual field assessment by Humphrey Automated perimetry (HFA), and optic nerve head evaluation by Optical Coherence tomography (OCT, by Zeiss Primus). Ocular surface disorder and dry eye was evaluated by Schirmer test 1 (SCH 1), Tear film break up time (TBUT), Conjunctival staining and OSDI questionnaire. OSDI questionnaire was used as a predesigned proforma to ask symptoms related to ocular surface disorders. 2% Fluorescein was instilled in the conjunctival cul de sac and fluorescein staining of conjunctival and corneal epithelium were evaluated semi quantitatively. Slit lamp examination was done to examine vital dye staining, determination of tear breakup time, Schirmer's testing, conjunctival reaction, meibomian gland dysfunction, and evaluation of the corneal epithelium. The most common ocular surface disorder, dry eye was defined as eyes having both positive vital staining (fluorescein score 1) and decreased tear function (Schirmer value 10 mm or less, or BUT less than 5 seconds). The effect of anti-glaucoma drops on the ocular surface was determined through clinical examination as well as through functional questionnaires to quantify the effects of ocular surface disease on patient quality of life. Participants diagnosed with primary open-angle glaucoma using topical hypotensive drug with no previous diagnosis of ocular surface disease were included.

SCH I test was performed using Schirmer's paper strip (Whatman 41 filter paper 5 X 35 mm strip) placed in the lateral lower conjunctival sac, at the junction of lateral one third and medial two third without topical anaesthesia. The patient is advised to look up and not to blink the eyes. The Schirmer strip was removed after 5 minutes and the length of the moistened area was recorded.

TBUT was used to measure tear quality. Sodium fluorescein dye instilled in the conjunctival sac and the average interval between last complete blink and the appearance of first dry spot on the precorneal film was calculated under cobalt blue filtered light. BUT is an indicator of mucin component of tears.

Conjunctival and corneal fluorescein staining was examined by instilling fluorescein dye in conjunctival culde sac. Examination is done on slit lamp with cobalt blue illumination. The interpalpebral conjunctival staining of temporal and nasal conjunctiva was graded using the Oxford Scheme 6-point scale (from 0 to 5). The grading of keratoconjunctival staining was mild (stage 0 or 1), moderate (stage 2 or 3), or severe (stage 4 or 5) [13].

Ocular Surface Disease Index [OSDI] questionnaire was used to assess quality of life. It is a 12 item questionnaire created by Allergan, Irvine, CA, to estimate the effect of dry eye symptoms on daily visual function [14]. This questionnaire is divided into three subscales: ocular symptoms, vision-related function, and environmental triggers. Patient responses are rated on a 0 to 4 scale with 0 corresponding to "none of the time" and 4 corresponding to "all of the time." Calculation of final score is done which ranges from 0 to 100 .Scores 0 to 12 represents normal, 13 to 22 represents mild dry eye disease, 23 to 32 represents moderate dry eye disease, and greater than 33 represents severe dry eye disease [15]. The total score is calculated through the formula: (sum of the score for all the questions answered) x 100/number of questions answered x 4. Higher OSDI scores are associated with worsening of ocular surface symptoms and advancing visual field loss in glaucoma patients [16].

All patients received a complete eye examination including measurement of IOP by Goldmann applanation tonometry, gonioscopic evaluation of angle of anterior chamber and optic disc evaluation before the study. Schirmer I, tear film breakup time (TBUT),

staining scores, and OSDI, a 12 item questionnaire were evaluated before and during 12-month-follow-up period at 1st, 3rd, 6th, and 12th months.

The collected data were coded and entered into an excel software (Microsoft office Excel 2010) database. Data analysis was done using Statistical Package for Social Sciences, version 16.0 (SPSS, Inc., Chicago, IL, USA) and Paired t test was used to compare quantitative variables. The values of <0.05 were considered statistically significant.

Results:

A total of 100 eyes of 50 patients of Primary open angle glaucoma were enrolled in the study. Mean age of patients was 57.27 years with 57 % males and 43% females. Table 2 - 6 illustrates that the during the subsequent visits at 3, 6 and 12 months, there were detectable changes in Schirmer I and TBUT tests indicating dry eye. There was statistically significant difference in mean SCH I test results between the groups at any time of the study and also there was significant TBUT change in different groups at different intervals. There was a significant difference from the baseline corneal and temporal conjunctival staining. Staining was higher in different groups at 3rd, 6th and 12th month. Significant difference was noted in OSDI questionnaire in different groups at 3rd, 6th and 12th month. IOP was decreased significantly in all of the groups at 1st, 3rd, 6th, and 12th months visits compared to baseline.

Table No.1: Frequency distribution of patients and total eyes enrolled for the study

Groups	No. of patients enrolled	No. of eyes enrolled
1A	8	16
1B	13	26
2A	6	12
2B	7	14
3A	9	18
3B	7	14

Table No. 2: Average Ocular Surface Parameters at the Time of Enrolment

Groups	SCH 1	TBUT	Staining	OSDI questionnaire
1A	18mm	14 seconds	Grade 0	10
1B	16mm	14 seconds	Grade 0	11
2A	20mm	18 seconds	Grade 0	9
2B	16mm	15 seconds	Grade 0	10
3A	18mm	16 seconds	Grade 0	11
3B	18mm	15 seconds	Grade 0	11

Table No. 3: Average Ocular Surface Parameters at- 1 Month

Groups	SCH 1	TBUT	Staining	OSDI questionnaire
1A	17mm	13 seconds	Grade 0	13
1B	14mm	12 seconds	Grade 1	15
2A	20mm	15 seconds	Grade 0	12
2B	14mm	13 seconds	Grade 0	14
3A	16mm	16 seconds	Grade 0	15
3B	14mm	14 seconds	Grade 1	18

Table No. 4: Average Ocular Surface Parameters at- 3 Months

Groups	SCH 1	TBUT	Staining	OSDI questionnaire
1A	15 mm	12 seconds	Grade 1	16
1B	12 mm	12 seconds	Grade 2	15
2A	18 mm	13 seconds	Grade 1	14
2B	11mm	12 seconds	Grade 2	18
3A	12 mm	14 seconds	Grade 2	21
3B	10mm	10 seconds	Grade 2	24

Table No. 5: Average Ocular Surface Parameters at- 6 Months

Groups	SCH 1	TBUT	Staining	OSDI questionnaire
1A	11mm	12 seconds	Grade 1	18
1B	10mm	10 seconds	Grade 2	17
2A	13mm	12 seconds	Grade 1	16
2B	10mm	10 seconds	Grade 2	20
3A	11mm	12 seconds	Grade 2	24
3B	10mm	9 seconds	Grade 3	28

Table No. 6: Average Ocular Surface Parameters at- 12 Months

Groups	SCH 1	TBUT	Staining	OSDI questionnaire
1A	10mm	11 seconds	Grade 1	20
1B	9mm	10 seconds	Grade 2	22
2A	12mm	10seconds	Grade 2	19
2B	9 mm	9 seconds	Grade 3	20
3A	9 mm	9 seconds	Grade 3	27
3B	8mm	8 seconds	Grade 3	32

Discussion:

The only modifiable risk factor in the management of glaucoma is IOP, which can be regulated by medical management. The current common therapies for the topical management of glaucoma include prostaglandin analogues, beta-adrenergic blockers, alpha-adrenergic agonists, and topical carbonic anhydrase inhibitors. The topical antiglaucoma treatment for glaucoma can cause or worsen ocular surface disease due to either the added preservative or the active ingredient of the medication itself. The ocular surface disease appears to increase in severity as the duration of therapy increases [17]. The majority of glaucoma patients require combination of topical
intraocular pressure (IOP) lowering agents, and around 49% of
ocular hypertensives may require two topical antiglaucoma medications within five years of diagnosis, thus increasing the risk of ocular surface disease. Ocular surface disease is also linked to a higher rate of failure in subconjunctival glaucoma surgery [18]. Therefore, the management of ocular surface disease in glaucomatous patients is very important to reduce further ocular morbidity and to improve the success of glaucoma therapy. Correspondingly, ocular surface disease appears to increase in severity as the duration of therapy and the number of glaucoma medications increases [19]. Each class of medication has specific potential adverse effects on the ocular surface. A higher prevalence and severity of obstructive meibomian gland dysfunction is seen with Prostaglandin analogues. Beta blockers reduce basal tear turnover rate by acting on beta receptors in the lacrimal gland. The mucus composition in the tear film is altered by Timolol and it also increases staining of the cornea and conjunctiva after one month of therapy. Brimonidine tartrate which is a commonly used alpha-adrenergic agonist has a significantly higher incidence of ocular allergy compared to other topical medications and it may also predispose patients to ocular allergy from additional topical antiglaucoma drops. The ocular surface disease in patients with glaucoma can lead to poor medication compliance [20]. Preservatives prevent microbial contamination of the drops by targeting bacterial cell walls and increasing drug penetration in the cornea [21], thus they are added to IOP lowering medications at the lowest concentration possible. As per Hollo et al. glaucoma therapy-related ocular surface disease is defined as, “imbalance of the ocular surface homeostasis caused by the toxic effect of chronic topical medication, which leads to tear film instability, epithelial damage, and inflammation”. [22] The observations of this study are consistent with Rossi et al. who reported that abnormal TBUT and punctuate keratitis, was more frequent with increasing number of eye drops and number of instillations per day in the patients with topically treated glaucoma [23]. In a Prospective, observer-masked study in 2012, conducted on 60 eyes of 30 open angle glaucoma patients, Januleviciene et al demonstrated, significant change in mean TBUT and abnormal fluorescein staining on intermediate-term use of antiglaucoma drugs [24], which was also noticed in our study. We measured tear quality with TBUT, tear production with SCH I test and evaluation of ocular surface by corneal and interpalpebral conjunctival staining. Our findings suggest that there was statistically significant difference in mean SCH I test values between the groups at any time of the study. TBUT decreased significantly in groups 3A (travoprost without preservative) and group 3B (travoprost with preservative) during the study. Schirmer value were reduced, as seen in group 2B, 3A and 3B at 6th and 12

months. Stewart et al. showed that timolol maleate demonstrated increased staining in the cornea and nasal conjunctiva from baseline to hour 0 and hour 1 on the healthy subjects [25], similar changes were observed over a period in present study. OSDI questionnaire scores showed that significant number of patients had severe symptoms, which is also shown in other studies [26]. The OSDI score limits itself by assessing a small number of dry eye symptoms including sensitivity to light, grittiness, and pain. It does not assess other symptoms like tearing ,foreign body sensation etc.

The OSDI questionnaire has demonstrated good specificity (0.83) and a moderate sensitivity (0.60) when distinguishing between patients with dry eye disease and normal subjects [27]. The preservative Benzalkonium Chloride (BAK) which is used frequently, plays an important role in ocular surface damage and the side effects are dose and time-dependent, more so in combined medications. Good periodic clinical evaluation and prevention of ocular injury should be seriously taken into consideration in the medical management of glaucoma. The development of complex preparations, preservative free and/or novel preservative preparations for glaucoma therapy could provide a promising approach in the prevention of ocular surface injury [28]. The limitations of our study are small sample size, short follow-up period and the factors that can affect ocular surface parameters such as humidity and seasonal effects.

Conclusion:

Our study concluded that the use of topical antiglaucoma drugs have association with ocular surface disorders. The ocular surface disorder may occur due to active ingredient or due to preservative in the drug. OSD in glaucoma patients may be minimized by preferable use of preservative free antiglaucoma drugs.

Conflict of Interest - Nil
Sources of Support - Nil

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Address for correspondence: *Dr. Ausaf Ahmad. Statistician cum Assistant Professor, Department of Community Medicine, Integral Institute of Medical Sciences and Research, Integral University, Lucknow, UP, India.*
Email: ausafahmad86@gmail.com.
Mobile: +91 8318240461.

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