Scholars Journal of Applied Medical Sciences (SJAMS)
Abbreviated Key Title: Sch. J. App. Med. Sci.
ISSN 2320-6691 (Online)
ISSN 2347-954X (Print)

A Unit of Scholars Academic and Scientific Society, India
www.saspublishers.com

Ophthalmology

Ocular Surface Disease Related to Prostaglandin Analogue with Benzalkonium Chloride versus Prostaglandin Analogue with Stabilized Oxy Chloride Complex in Glaucoma Patients

Dr. Snehal Pophali[1], Dr. Chandan Tiple[2*]
[1]Resident, Department of Ophthalmology, Govt Medical College, Chandrapur, Maharashtra, India
[2]Assistant professor, Department of Ophthalmology, Govt Medical College, Chandrapur, Maharashtra, India

Original Research Article

***Corresponding author**
Dr. Chandan Tiple

Article History
Received: 14.12.2018
Accepted: 24.12.2018
Published: 30.12.2018

DOI:
10.36347/sjams.2018.v06i12.043

Abstract: To evaluate the effects of travoprost with Benzalkonium chloride(BAC) versus travoprost with Stabilized Oxy chloride complex(SOC) on ocular surface in case of primary open angle glaucoma (POAG). Our study involved 56 patients (112 eyes) who received antiglaucomatous treatment by instillation of one drop of travoprost (0.004%) with SOC (0.005%) group 1 (56 eyes of 28 patients) and travoprost with BAC (0.015%) group 2 (56 eyes of 28 patients) every 24 hours. Patients completed Ocular Surface Disease Index questionnaire, underwent evaluation by Schirmer test, tear breakup time, corneal and conjunctival fluorescein and lissamine green staining. In group 1-at the end of 6 months, 14.28% eyes were abnormal in schirmer test, 23.21% in TBUT, 28.57% had abnormal scoring in both staining, mild to moderate OSDI score was seen in 53.57% and severe OSDI score in 14.28%. In group 2- 19.64% eyes were abnormal in schirmer test, 55.35% in TBUT, 39.2% had abnormal scoring in both staining, mild to moderate OSDI score was seen in 57.14% and none of the patients had severe OSDI score. High prevalence of ocular surface diseases was noted in patients using travoprost with Benzalkonium chloride as compared with travoprost with Stabilized Oxy chloride complex. Ocular surface disease must be kept in mind in symptomatic patients as it is likely to affect drug compliance.
Keywords: OSDI score, ocular surface disease, Tear breakup time (TBUT), Prostaglandin analogue.

INTRODUCTION

Glaucoma is the second leading cause of blindness in the world and is predicted to account for over 11 million by 2020 [1]. Medical treatment is considered an effective way of controlling glaucoma in its initial stage [2]. Topical medical treatments are mainly used as first-choice therapy to avoid the onset of further irreversible optic nerve damage and visual field defects. Most of the patients are on long term treatment medically. Surgery is reserved in case of intolerance, inadequate response to topical therapy or progression. Side effects need to be minimised to promote compliance and allow continuation of long-term therapy. The benefits of reducing microbial contamination through use of preservatives are offset by the known ocular side effects of preservatives [3]. The toxic action of preservatives on the ocular surface has been widely demonstrated in vitro as well as in vivo, in both humans and animals [4-6].

Benzalkonium chloride (BAC) is among the most common preservatives used in ophthalmic preparations. Benzalkonium chloride kills bacteria; the same mechanism that eradicates microbes is also toxic to many cell types of the eye. The ocular effects are dose-dependent and can range from apoptosis to necrosis. The local inflammation causes changes that can mimic the appearance of dry eye signs and symptoms. The discomfort associated with dry eye decreases patients' quality of life, and it also reduces their desire to comply with treatment [7].

Oxidants, such as stabilized oxychloro complex (SOC) and sodium perborate, are usually small molecules that penetrate cell membranes and disrupt cellular function by modifying lipids, proteins, and DNA. Their membrane destabilizing activity is less potent than that of detergent preservatives. At low levels, oxidative preservatives have an advantage over the detergent preservatives by providing enough activity against microorganisms while exerting only negligible toxic effects on eukaryotic cells [8].

The aim of our study was to evaluate the signs and symptoms of OSD in POAG patients treated with travoprost with BAC versus travoprost with SOC.

METHODS

Our study involved 56 patients (112 eyes) who received antiglaucomatous treatment in primary open angle glaucoma patients by instillation of one drop of travoprost (0.004%) with SOC (0.005%) and travoprost with BAC (0.015%) every 24 hours. These patients were not receiving any other topical ocular treatment. Patients were excluded with history of ocular surgery, previous topical drug administration within last 3 months, ocular surface disease, and collagen vascular disease, known hypersensitivity to therapy, contact lens use and allergic conjunctivitis.

The diagnosis of glaucoma was confirmed by Applanation tonometry, gonioscopy, visual fields defect (GHT outside normal limits and/or PSD with p<5%), OCT and fundus examination for glaucomatous optic neuropathy (rim thinning, excavation and/or retinal nerve fibre layer defects). Informed and written consent was obtained from all patients with consent form approved by the institutional ethical committee.

Patients were divided into two groups: Group 1(56 eyes of 28 patients): Patients on Travo-Z with stabilised Oxychloro complex (0.005%). Group 2 (56 eyes of 28 patients): Patients on Travatan (0.004%) with Benzalkonium chloride (0.015%).

Demographic information, brief medical history and information on concomitant medicine use were obtained from patient's medical records. Visits were scheduled at 1 ½, 3rd and 6th month.All the eligible patients were asked to complete Ocular Surface Disease Index [OSDI] questionnaire. After completing the OSDI questionnaire, patients under went three standard clinical tests for the detection of ocular surface disorder – Schirmer test, Tear breakup time (TBUT) and Fluorescein and Lissamine green staining of conjunctiva and cornea which were repeated on each follow-up visits.

The OSDI questionnaire was designed as a screening survey to assess symptoms and their impact on vision related function [9]. The 12 questions of OSDI questionnaire were graded on the scale of 0 to 4. 0 – none of the time, 1 – some of the time, 2 – half of the time, 3 – most of the time, 4 – all the time. The total OSDI score was calculated using the formula

OSDI= [(sum of scores for all questions answered)×100]/[(total number of questions answered)×4. Thus, the OSDI was scored on a scale of 0 to 100.

To maximize the sum of the sensitivity and specificity values, the severity designations used for the OSDI score were as following: 0 to 5.9, normal; 6.0 to 14.9, mild to moderate; and >=15.0, severe.

Schirmer's test I was done with Schirmer's paper (5x35mm) inserted in the inferior fornix at the junction of lateral and middle thirds of the lower eyelid for 5 min. Then the filter paper was removed and the amount of wetting was measured. This test gave the value for both basic and reflex secretions of tears. The severity designations used for the Schirmer test were the following: >10 mm, normal; 6 to 10 mm, mild to moderate; and 0 to 5 mm, severe.

Tear film instability was evaluated by performing a tear breakup time (TBUT)test. Method used involved instillation of fluorescein dye into the eye. After the dye was distributed throughout the tear film by blinking, the patient was asked to stare straight ahead without blinking. Under slit-lamp examination, the time between the last blink and the appearance of the first break in the fluorescent tear film was measured. Values of <10 seconds was considered abnormal.

Fluorescein staining: 2% fluorescein strip was applied to lower fornix for few Seconds and examined using cobalt blue filter. Score - 0 for absent, 1 for just present, 2 for moderate staining and 3 for gross staining. A total score of more than 3 out of 9 is considered abnormal

Lissamine staining: Lissamine strip applied to lower fornix for few seconds. Using white light of moderate intensity, staining at the corneal region and the interpalpebral region of the nasal and temporal conjunctiva was graded using the Oxford Scheme. Corneal and conjunctival lissamine green staining was evaluated after 30 seconds but before 2 minutes had elapsed after instillation. The severity designations used for lissamine green staining using the Oxford scheme were the following: 0 to I-normal; II to III-mild to moderate; and IV to V- severe.

STATISTICAL ANALYSIS

A total of 56 patients (112 eyes) were included in the study. The data was entered in MS EXCEL spread sheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0. A paired test was used to assess the changes at baseline and at 6 months. A Chi square test was applied to find out difference of results between two groups at the end of the 6 months. P-value has been calculated using two tailed test. A p-value of less 0.05 is considered significant.

RESULTS

All results are provided as means and standard deviations for continuous variables and frequencies and percentages (%) for ordinal variables, unless otherwise indicated. The overall mean age of the patient was 57.14 years in group 1 and 54.75 years in group 2.

Approximately two-thirds of the patients were females (62.5%). (60.71%) females in group 1 and (64.28%) females in group 2.Results obtained from OSDI questionnaire and three tests are summarized in table 1 and graph1 (1a, 1b, 1c, 1d).

The OSDI score in group 1- 32.14% patients were normal, 53.57% were mild to moderate and 14.28 % had severe dry eyes. In group 2, at 6 months 42.85% were normal, 57.14% had mild to moderate dry eyes and none of the patients were severe.

Schirmer's test value of more than 10 mm is considered normal and that of less than 10 mm is considered abnormal. In group 1, 0% eyes were abnormal at baseline and 14.28% at 6 months. (p=0.003) In group 2, 0% eyes were normal at baseline compared to 19.64% at 6 months. (p=0.0006) Fisher exact test was applied and there was no statistically significant difference between both groups. (p=0.6217)

The value of TBUT is taken as normal if it is above 10 seconds and abnormal if it is less than 10 seconds. In group 1, the tear film break up time at baseline wasabnormal in 0% eyes and at 6 months it wasabnormal 23.21% of eyes. (P=0.00002) In group 2, the tear film break up time at baseline wasabnormal in 0 % eyes compared to 55.35% at 6 months (p=<0.00001).Fisher exact test was applied and there was statistically significant difference between both groups. (p=0.002)

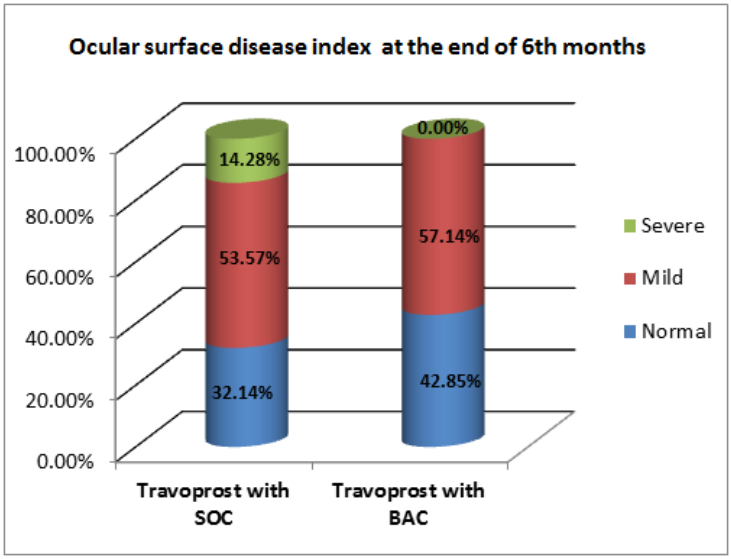
Flourescein staining graded according to Van Bijeterveld Scheme-Normal: Score < 3 and abnormal: score ≥ 3. In group 1, 0% of eyes at baseline had anabnormal score while at 6 months only 28.57% had abnormal score.(p=0.000004).In group 2, 0% of eyes at baseline had abnormal score compared to 39.2% at 6 months. (p=0.0000002).There was no statistically significant difference between both groups. (p=0.43)

Lissamine green dye staining is graded according to the OXFORD GRADING SCHEME. Normal = grade 0 and I and Abnormal = grade II – V. In group 1, 0% of eyes at baseline had abnormal score while at 6 months only 28.57% had an abnormal oxford scheme score.(p= 0.000004) In group 2, 0% of eyes at baseline had an abnormal score compared to 39.2% at 6 months(p=0.0000002).There was no statistically significant difference between both groups. (p=0.43) (Figure 1).

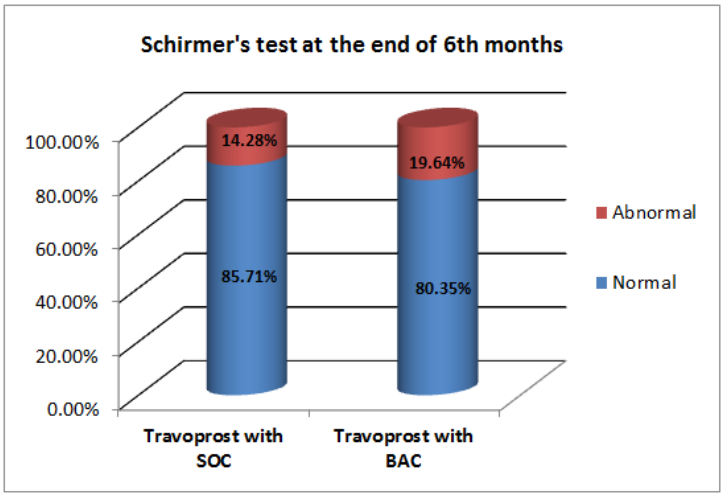
Table-1: Comparison of OSDI questionnaire and three tests (Schirmer's test, TBUT and staining) between Travoprost with SOC and Travoprost with BAC groups

Treatment Group	Visit	OSDI			Schirmer's test		TBUT		Fluorescein staining		Lissamine staining	
		Normal (0-5.9)	Mild (6-14.9)	Severe (>15)	Normal (>10 mm)	Abnormal (<10 mm)	Normal (>10 secs)	Abnormal (<10 secs)	Normal score <3	Abnormal score ≥3	Normal Grade 0-I	Abnormal Grade II-IV
Travoprost with SOC	Baseline	50.0%	42.8%	7.1 %	100%	0%	100 %	0%	100%	0%	100%	0%
	1 ½ Months	35.71 %	57.14 %	7.1 %	100%	0%	100 %	0%	98.21%	1.78 %	98.21 %	1.78%
	3 Months	32.14 %	57.14 %	10.71%	94.64 %	5.35 %	96.42%	3.58 %	91.00%	8.92 %	91.00 %	8.92%
	6 Months	32.14 %	53.57 %	14.28%	85.71 %	14.28 %	76.78%	23.21 %	71.42%	28.57 %	71.42 %	28.57%
Travoprost with BAC	Baseline	46.42 %	53.57 %	0%	100%	0%	100 %	0%	100%	0%	100%	0%
	1 ½ Months	42.85 %	57.14 %	0%	100%	0%	100 %	0%	100%	0%	100%	0%
	3 Months	42.85 %	57.14 %	0%	89.2%	10.71 %	83.92%	16.07 %	100%	0%	100%	0%
	6 Months	42.85 %	57.14 %	0%	80.35 %	19.64 %	44.64%	55.35 %	62.5%	39.2 %	62.5%	39.2%

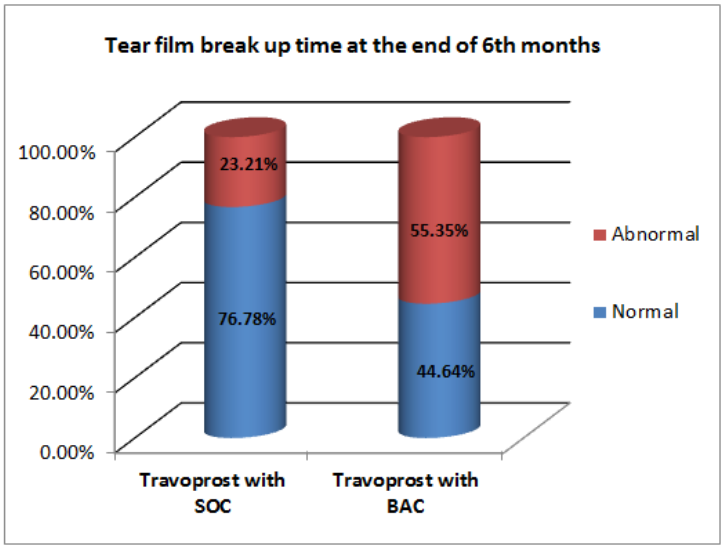
OSDI- Ocular surface disease index; TBUT – tear film break up time; % (no of eyes)



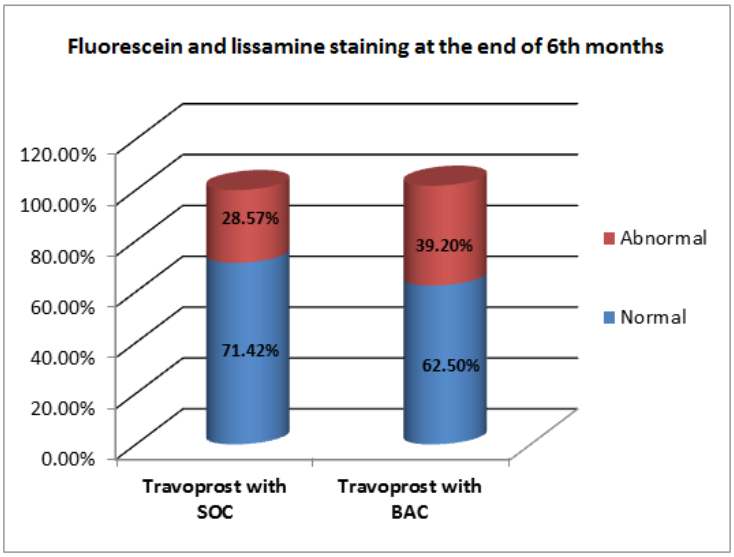
Graph-1a



Graph-1b



Graph 1c



Graph 1d

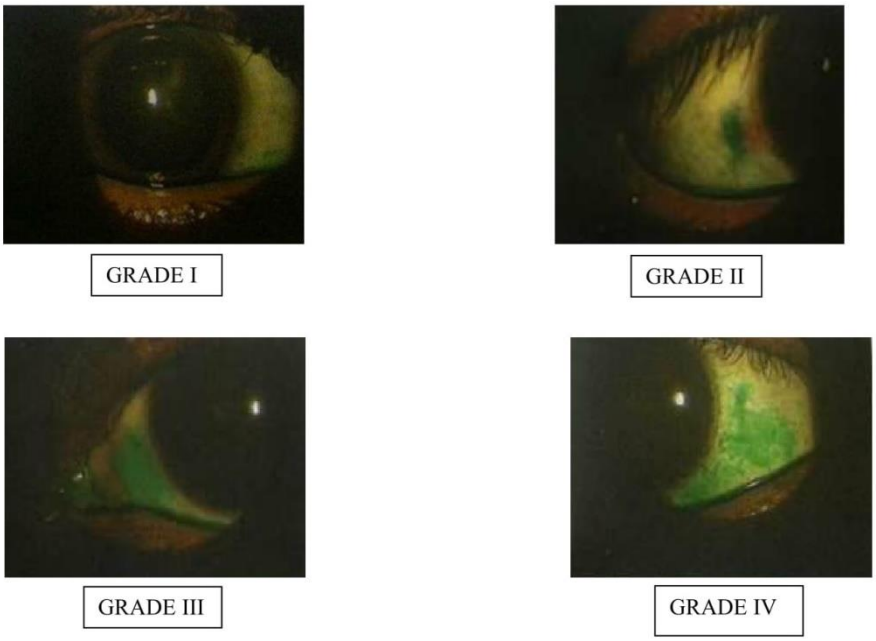


Fig-1: Lissamine Staning of patients treated with travoprost

DISCUSSION

The prevalence of both glaucoma and Ocular surface disease is increasing as the population ages [10]. Chronic uses of topical anti-glaucoma ophthalmic products for the treatment of glaucoma often contribute to the development or worsening of OSD.

BAC is the most common preservative used in commercially available eye drops. Ophthalmic preservatives help prevent bacterial contamination and prolong the shelf life by limiting bio-degradation and maintaining drug potency. When used chronically, preservatives can disrupt the precorneal tear film and lead to damage of the ocular surface and worsening of OSD symptoms.The mechanism of side effects caused by antiglaucoma medication on the ocular surface and tear film secretion are unclear. They may be due to preservatives and / or active compounds.

At the end of 6 months, abnormal schirmer's test value was seen in 14.28% eyes in Travoprost with SOC group and 19.64% in Travoprost with BAC group. Almost equal number of eyes on Travo-Z and Travatan showed abnormal schirmer's test result at the end of 6 months.These findings suggest that the long term use of both the drugs is likely to affect the tear secretion.

Algoz *et al*. [11] in 2008 reported that tear film production did not differ from baseline in newly diagnosed glaucoma patients treated with either BAC

containing Bimaprost or Travoprost for 6 months. Martone G. *et al*.[12]. In 2009 with study of effect of topical antiglaucoma therapy with preservative showed 19% decrease in tear production. Study in 2008 by Leung EW and Medeiros FA *et al*. [13] for prevalence of ocular surface disease in glaucoma patients showed decrement in tear production by schirmer testing in 35% eyes with BAC preserved Timolol. Bonomi L *et al*. [14] study, Timolol Maleate affects corneal sensitivity, and decreased corneal sensitivity results in a decreased blink rate, which in turn brings about a decrease in tear turnover. Kuppens *et al*. [15] have studied that basal tear turnover rate using flurophotometry in patients who had used Timolol Maleate 0.5% for duration of 3.5 years and observed that the basal tear turnover is slightly decreased in Timolol Maleate with BAC group as compared to controls and the group administered with Timolol Maleate without BAC.

Significantly abnormal TBUT results were seen in both groups. However, the Travatan group showed a larger percentage of abnormal changes as compared to the Travo-Z group.Exposure to BAC causes decrease in goblet cell density and alters the precornealmucin which is important in maintaining the integrity of the tear film.

Wilson *et al*. [16] demonstrated that 0.01% BAK hastened the drying of precorneal tear film in rabbits and man.The two studies by Ishibashi T, Yokoi N *et al*. [17]. In 2003 and ShimazakiJ, Hanada K *et al*. [18] in 2000 for the effect of antiglaucoma medication with and without preservatives showed decrease in tear film stability with preservatives by 17 and 40% respectively. Baudouin C *et al*. [19] found that albino rabbits given a preserved blocker (Timoptol 0.25% and 0.5%; preserved with 0.01% BAC) displayed a significantly greater reduction in TBUT compared with those given a non-preserved beta blocker.

Fluorescein and Lissamine staining at the end of 6 months was significantly abnormal in both Travo-Z and travatan groups 28.57% and 39.2% respectively, but difference in the two groups was not statistically significant.In 2007 by Lewis RA, Katz GA. [20] *et al*. a 3 month study of comparison of effects of travoprost with and without BAC found that mild to moderate conjunctival staining was noted in 0.3% eyes in BAC free group and in 1.2% eyes in BAC group. Study in2008 by Leung EW and Medeiros FA *et al*. [21] for prevalence of ocular surface disease in glaucoma patients demonstrated corneal and conjunctival Lissamine green staining in 22% of patients but none was scored serious.

Normal OSDI score was seen in 32.14% patients at the end of 6 months in group 1 and 42.85% in group 2.Mild to moderate OSDI score was seen in 53.57% patients in group 1 and 57.14% in group 2.Severe OSDI score was seen in 14.28% in group 1 but 0% in group 2.

In 2010 study by Katz *et al*. [22] concluded that switching from BAC preserved Latanoprost to BAC free Travoprost yielded significant improvement in symptoms of OSD.In 2008 Henry *et al*. [23] with similar study concluded that patients previously treated with BAC preserved PG analogue switched to Travoprost BAC free drug have clinically and statistically significant improvement in their OSDI score.None of the patients required discontinuation of drugs due to the presence of symptoms.

We also investigated the relationship between OSD symptoms based on OSDI questionnaire and clinical signs.A large proportion of patients who reported symptoms on the OSDI questionnaire had normal results on the clinical tests. Conversely, a large proportion of patients with abnormal results on clinical tests had normal results on OSDI questionnaire.This is in agreement with previous studies done by Schein *et al*. [24] and Hay EM *et al*. [25] that has also found a poor correlation between objective and subjective signs of OSD.Also it can be due to the decreased sensation of cornea due to loss of afferents with the long term use of BAC leading to fewer symptoms noted by the patient.

Prostaglandin analogs have progressively replaced beta-blockers as the first-line therapy of POAG, because they are the most effective IOP-lowering agents, lack relevant systemic side effects, and require only once-daily dosing.[26,27]Preservative-free prostaglandin analogs – such as travoprost – minimize the risk of ocular side effects and increase the likelihood of good treatment adherence. Hence, preservative-free solutions should be considered when available. They could be particularly beneficial to patients who 1) have pre-existing ocular surface disease, 2) are expected to develop ocular surface disease (dry eye) during long-term medication, 3) are using multiple concomitant topical ocular treatments, and/or 4) are about to undergo glaucoma surgery[28,29]. In general, the current glaucoma treatment guidelines call for therapies that can maintain visual function, minimize side effects, increase adherence, and improve quality of life of the patients. A correct choice of first-line therapy is fundamental to achieving these patient outcomes and reducing the economic costs in the long run. Preservative-free prostaglandin analogs currently provide the best monotherapy option for first-line treatment of POAG. The costs of disease management could even be halved, if POAG is prevented/delayed effectively [30]. Limitation of our study was small sample size and short duration of follow-up period.

CONCLUSION

. Thus, Stabilised Oxychloro Compound preservative in Travoprost preserves the ocular surface

integrity better compared to Benzalkonium chloride in the Travoprost though the adverse effects of original drug molecule could not be negated in both groups. Ocular surface disease must be kept in mind in symptomatic patients as it is likely to affect drug compliance.

REFERENCES

1. Quigley HA, Broman A. The number of persons with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol. 2006; 90:151-156.
2. Bohn RL, Gurwitz JH, Yeomans SM, Glynn RJ, Pasquale LR, Walker AM, Avorn J. Which patients are treated for glaucoma? An observational analysis. Journal of glaucoma. 2000 Feb;9(1):38-44.
3. Wilcon LA. To preserve or not to preserve, is that the question? Br J Ophthalmol. 1996; 80: 583-4.
4. De Saint Jean M, Debbasch C, Brignole F, Rat P, Warnet JM, Baudouin C. Toxicity of preserved and unpreserved antiglaucoma topical drugs in an in vitro model of conjunctival cells. Current eye research. 2000 Jan 1;20(2):85-94.
5. Burstein NL. Corneal cytotoxicity of topically applied drugs, vehicles and preservatives. SurvOphthalmol. 1980; 25:15-30.
6. Burstein NL. The effects of topical drugs and preservatives on the tears and corneal epithelium in dry eye. Trans ophthalmolSoc UK. 1985; 104 :402-9.
7. Noecker R. Effects of common ophthalmic preservatives on ocular health. Ad Ther. 2001; 18:205-215.
8. Asbell PA, Potapova N. Effects of topical antiglaucoma medications on the ocular surface. The ocular surface. 2005 Jan 1;3(1):27-40.
9. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the ocular surface disease index. Archives of ophthalmology. 2000 May 1;118(5):615-21.
10. Bagnis A, Papadia M, Scotto R, Traverso CE. Antiglaucoma drugs: the role of preservative-free formulations. Saudi Journal of Ophthalmology. 2011 Oct 1;25(4):389-94.
11. Alagöz G, Bayer A, Boran Ç, Serin D, Kükner A, Elçioğlu M. Comparison of ocular surface side effects of topical travoprost and bimatoprost. Ophthalmologica. 2008;222(3):161-7.
12. Martone G, Frezzotti P, Tosi GM, Traversi C, Mittica V, Malandrini A, Pichierri P, Balestrazzi A, Motolese PA, Motolese I, Motolese E. An in vivo confocal microscopy analysis of effects of topical antiglaucoma therapy with preservative on corneal innervation and morphology. American journal of ophthalmology. 2009 Apr 1;147(4):725-35.
13. Leung EW, Medeiros FA, Weinreb RN. Prevalence of ocular surface disease in glaucoma patients. Journal of glaucoma. 2008 Aug 1;17(5):350-5.
14. Bonomi L, Zavarise G, Noya E, Michieletto S. Effects of timolol maleate on tear flow in human eyes. Graefe's Archive for Clinical and Experimental Ophthalmology. 1980 Mar 1;213(1):19-22.
15. Kuppens EV, de Jong CA, Stolwijk TR, De Keizer RJ, Van Best JA. Effect of timolol with and without preservative on the basal tear turnover in glaucoma. British journal of ophthalmology. 1995 Apr 1;79(4):339-42.
16. Wilson WS, Duncan AJ, Jay JL. Effect of Benzalkonium chloride on the stability of the precorneal tear film in rabbit and man. Br J Ophthalmol. 1975; 59: 667-9.
17. Ishibashi T, Yokoi N, Kinoshita S. Comparison of the short-term effects on the human corneal surface of topical timolol maleate with and without benzalkonium chloride. Journal of glaucoma. 2003 Dec 1;12(6):486-90.
18. Shimazaki J, Hanada, Yagi Y et al. Changes in ocular surface caused by antiglaucomaeyedrops: prospective, randomized study for the comparison of 0.5 % Timolol Maleate Vs. 0.12% Unoprostone. Br J Ophthalmol 2000; 84: 1250-1254.
19. Baudouin C, Pisella PJ, Fillacier K, Goldschild M, Becquet F, De Saint Jean M, Béchetoille A. Ocular surface inflammatory changes induced by topical antiglaucoma drugs: Human and animal studies1. Ophthalmology. 1999 Mar 1;106(3):556-63.
20. Lewis RA, Katz GJ, Weiss MJ, Landry TA, Dickerson JE, James JE, Hua SY, Sullivan EK, Montgomery DB, Wells DT, Bergamini MV. Travoprost 0.004% with and without benzalkonium chloride: a comparison of safety and efficacy. Journal of glaucoma. 2007 Jan 1;16(1):98-103.
21. Leung EW, Medeiros FA, Weinreb RN. Prevalence of ocular surface disease in glaucoma patients. Journal of glaucoma. 2008 Aug 1;17(5):350-5.
22. Katz G, Springs CL, Craven ER, Montecchi-Palmer M. Ocular surface disease in patients with glaucoma or ocular hypertension treated with either BAK-preserved latanoprost or BAK-free travoprost. Clinical ophthalmology (Auckland, NZ). 2010;4:1253.
23. Henry JC, Peace JH, Stewart JA, Stewart WC. Efficacy, safety, and improved tolerability of travoprost BAK-free ophthalmic solution compared with prior prostaglandin therapy. Clinical ophthalmology (Auckland, NZ). 2008 Sep;2(3):613.
24. Schein OD, Tielsch JM, Muñoz B, Bandeen-Roche K, West S. Relation between signs and symptoms of dry eye in the elderly: a population-based perspective. Ophthalmology. 1997 Sep 1;104(9):1395-401.
25. Hay EM, Thomas E, Pal B, Hajeer A, Chambers H, Silman AJ. Weak association between subjective symptoms of and objective testing for dry eyes and dry mouth: results from a population based study. Annals of the rheumatic diseases. 1998 Jan 1;57(1):20-4.

26. European Glaucoma Society. Terminology and Guidelines for Glaucoma. 4th ed. Savona: PubliComm. 2014:141–142.
27. Boland MV, Ervin AM, Friedman DS, Jampel HD, Hawkins BS, Vollenweider D, Chelladurai Y, Ward D, Suarez-Cuervo C, Robinson KA. Comparative effectiveness of treatments for open-angle glaucoma: a systematic review for the US Preventive Services Task Force. Annals of internal medicine. 2013 Feb 19;158(4):271-9.
28. Baudouin C. Detrimental effect of preservatives in eyedrops: implications for the treatment of glaucoma. ActaOphthalmol. 2008;86: 716–726.
29. Bagnis A, Papadia M, Scotto R, Traverso CE. Current and emerging medical therapies in the treatment of glaucoma. Expert OpinEmerg Drugs. 2011;16:293–307.
30. Denis P. Adverse Effects, Adherence and Cost–Benefits in Glaucoma Treatment. Adverse Effects, Adherence and Cost–Benefits in Glaucoma Treatment. 2011.