Clinical and Experimental Vision and Eye Research (2020), 3, 17–29

ORIGINAL ARTICLE

Evaluation and comparison of the safety profile of topical anti-glaucoma drugs in patients of primary open angle glaucoma or ocular hypertension or normal tension glaucoma

Purvi Raj Bhagat[1], Kinjal Yogesh Trivedi[2]

[1]Department of Ophthalmology, Head of Glaucoma Clinic, M and J Western Regional Institute of Ophthalmology, Ahmedabad, Gujarat, India, [2]Department of Ophthalmology, M and J Western Regional Institute of Ophthalmology, Ahmedabad, Gujarat, India

Key words:

Adverse event, anti-glaucoma medications, benzalkonium chloride, compliance, glaucoma, side-effects

Address for correspondence:
Dr. Kinjal Yogesh Trivedi, A/801, Ashima Towers, Opp. Sandesh Press, Bodakdev, Ahmedabad - 380 054, Gujarat, India.
Phone: 079-26852616/ +91-9409203143/+91-9898136258.
E-mail: kinjaltrivedi30@gmail.com

Received: 29-06-2020;
Accepted: 24-07-2020
doi: 10.15713/ins.clever.51

Abstract

Aim: The aim of the the study was to evaluate and to compare the side effects of topical anti-glaucoma drugs in patients of POAG, OHT, ad NTG.
Introduction: Topical drugs are the mainstay of glaucoma management but are associated with various adverse effects which can influence compliance and quality of life of the patient.
Materials and Methods: We studied 308 eyes of 154 patients above 15 years, having POAG, OHT, or NTG and using at least one anti-glaucoma medication. A structured validated questionnaire was used followed by ocular examination to collect data which were analyzed statistically.
Results: Out of 308 eyes of 154 patients, 80.51% patients experienced at least one side effect, more in females. The incidence increased to 72.52%, 92.10%, 91.66%, and 100% among 50–59, 60–69, 70–79, and 80–89 age groups, respectively. TBUT was normal in 62.79% eyes when duration of therapy was ≤ 5 years but not when beyond 11 years and normal only in 34% eyes exposed to benzalkonium chloride. Only 8.45% patients experienced systemic side effects but none required emergency care. Change of therapy due to side effects occurred in 8.11% patients.
Conclusion: Topical anti-glaucoma drugs are quite safe but incidence of side effects increases with age, duration of therapy, and number of medications. Although few, they affect the quality of life and compliance potentially limiting success of the treatment.
Clinical Significance: Knowledge of side effects helps us in tailoring, monitoring, and revising treatment as necessary, to minimize side effects and maximize outcomes.

Introduction

Glaucoma is a major public health problem and is the second major cause of blindness after cataract. More importantly it is the most common cause of irreversible blindness globally. It is estimated by the World Health Organization that around 4.5 million people are blind worldwide due to glaucoma.[1-3] It is also estimated that there are more than 60 million cases of glaucoma globally and will increase to 80 million by end of 2020.[1-3] By end of 2020, India, will become second overall in number with glaucoma, surpassing Europe. The estimated number of cases of glaucoma in India is 12 million, around one-fifth of the global burden of glaucoma.[4,5]

Glaucoma also has a serious impact on the quality of life of the affected people. The visual acuity and the visual field loss associated with the disease influence all daily activities such as walking, driving, reading, and household activities such as cooking, sewing, and others. Moreover, these losses are frequently associated with other serious consequences such as falls and road accidents. The impact further varies widely according to the stage of disease and the patient.[6] Hence, treatment should be sought early in the course of the disease to prevent further vision loss as well as to preserve the quality of life.

There are multiple options available for the treatment of glaucoma such as anti-glaucoma drugs of various classes, laser

procedures, and surgical modalities. The preferred first line of management is in the form of topical medications which are usually successful in controlling IOP in most patients but have to be used lifelong which might be a cause of concern in terms of cost and compliance for some patients. The topical drugs are also often associated with a variety of ocular side effects. It is recognized that eye drops containing benzalkonium chloride (BAK) especially when used chronically reduce the stability of tear film due to direct toxic effect, contributing to anterior segment symptoms lowering the therapy compliance. Some anti-glaucoma medications can also create cosmetic blemishes especially in young patients and when used unilaterally. Topical and systemic therapy for glaucoma can also lead to systemic adverse effects such as diuresis, headache, electrolyte imbalance, anaphylaxis, cardiovascular overload, intracranial hemorrhage, pulmonary edema, and renal failure.[7,8] These local and systemic side effects can further affect the quality of life of the patients directly and indirectly which can be overwhelming especially when the patient is on multiple drugs.

Our study attempts to evaluate and compare the side effects of various classes of topical glaucoma medications. Through our study, we also attempt to evaluate any influences of demographic characteristics on the side effects, establish correlation between BAK and resultant side effects and assess the acceptability of drug therapy inpatients. Such a thorough understanding can possibly help in better management of the patients, improving patient compliance, and preventing serious side effects.

Materials and Methodology

Ethical measures were adhered to throughout all phases of the research. The study was conducted among patients above the age of 15 years, attending our tertiary health-care referral center, who were diagnosed with either primary open angle glaucoma (POAG), normal tension glaucoma (NTG) or ocular hypertension (OHT), were on at least one anti-glaucoma medication and were willing to participate in the study. The duration of the study was from December 2016 to June 2018. Patients in whom any prior intervention for glaucoma had been done, those with pre-existing ocular or systemic allergy, known drug sensitivity, with known skin disease and using contact lenses were excluded from the study.

A structured validated questionnaire was administered as an interview to collect the data followed by a detailed clinical examination. For validation of our questionnaire, a pilot test was conducted on 30 eligible patients whose data have not been included in study analysis.

Informed consent was obtained from all the respondents before taking the interviews, with the purpose of the study explained, with emphasis on the fact that refusal to participate would not affect their future treatment. Respondents were also assured of confidentiality and privacy. We asked the same questions to all the participants in a precise manner, offering each individual the same set of possible responses. The questionnaire was also translated into Hindi and Gujarati and interviews were conducted in the language which the patients could understand.

Our questionnaire comprised following sections:

1. Preliminary/Demographic data
2. History of use of anti-glaucoma medications and changes in them during the course of therapy
3. History of use of concomitant drugs with their indications
4. Side effects experienced by patients (Local and Systemic)
5. Questions related to dry eye
6. History of emergency treatment for side effect
7. Overall acceptance of the drug.

Regarding their acceptability of respective drug therapy, we divided the patients into four groups – "Easily acceptable" (if patient had no complaints regarding therapy), "Moderately acceptable" (if the therapy was affecting their quality of life but was manageable and patient did not desire change of treatment),"Acceptable with difficulty" (if the therapy had a significant effect on their quality of life with a strong desire to change the mode of therapy), and "Not acceptable at all" (if the side effects were so severe that they were not bearable by the patient and warranted an immediate change of therapy).

Following the interview, a thorough ocular examination was done of each patient through best corrected visual acuity (BCVA), torch light, and slit lamp examination, followed by assessment for dry eye using Tear film breakup time (TBUT) and Schirmer's test type 1 and 2. As type 2 Schirmer's test with topical anesthesia, by way of its eliminating reflex tear secretion which can induce greater variation among individuals, is more objective and reliable than type 1 in diagnosing dry eye and therefore, we have given more importance to it while interpreting our results.[9]

The data were entered into Microsoft Excel sheet for further analysis. Percentage values were calculated and "Chi-square" test was used for statistical analysis wherever applicable.

Results

The study included 154 patients out of which 51 (33.11%) were males and rest 103 (66.88%) were females. Age of the patients was in the range of 40–87 years.

Out of 154 patients, 30 (19.48%) patients had no side effects which included 13 (43.33%) males and 17 (56.66%) females. The rest 124 (80.51%) patients experienced one or other side effect which included 38 (30.64%) males and 86 (69.35%) females [Figure 1].

In the age group 40–49 years, six out of 11 patients developed side effects suggesting an incidence of 54.54%. In age groups of 50–59, 60–69, and 70–79, the incidence of side effects increased to 72.52%, 92.10%, and 91.66%, respectively. The incidence of side effects was 100% in age group of 80–89 years. Thus, with increasing age group, the tolerability to anti-glaucoma medications seems to decrease and incidence of side effects increases [Figure 2].

Out of 118 eyes where single drug was used, only 58 (49.15%) developed side effects while in eyes treated with two drugs (106), the incidence of side effects was 97.16% and in eyes treated with three drugs (68) and four drugs (16), it was 100% [Figure 3].

When the duration of use of anti-glaucoma therapy was ≤5 years, TBUT values were normal, marginal, and low in, respectively, 108 (62.79%), 62 (36.04%), and 2 (1.16%) out of 172 eyes. The ratio of normal values decreased with simultaneous increase in marginal and low values with increasing duration of anti-glaucoma drug use. When the duration increased beyond 11 years, there was no eye showing a normal TBUT value. The TBUT values fall with increasing duration of use of anti-glaucoma medications which is statistically significant, with $P < 0.00001$, the result being significant at $P < 0.01$ [Table 1].

When the duration of use of anti-glaucoma therapy was ≤5 years, values of Schirmer's test type 2 were normal and positive in, respectively, 100 (58.13%) and 72 (41.86%) out of 172 eyes. The proportion of normal values decreased to 21 (19.81%) when duration of anti-glaucoma therapy was between 6 and 10 years and eyes with positive Schirmer's test increased to 85 (80.18%) out of 106 eyes. Beyond 11 years of use, all the eyes showed a positive Schirmer's test, though no eyes had values correlating with a strongly positive Schirmer's test. $P < 0.00001$, the result being significant at $P < 0.01$ [Table 2].

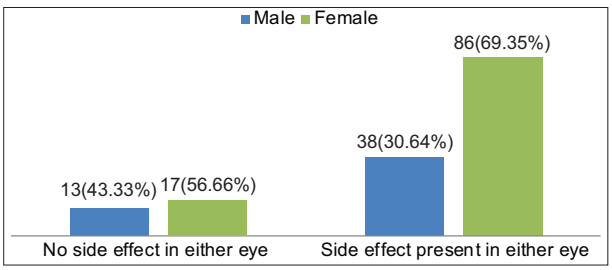

Figure 1: Association of incidence of side effects with gender of patients

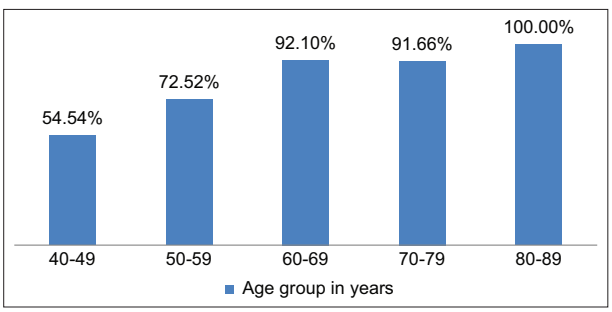

Figure 2: Association of incidence of side effects with age group of patients

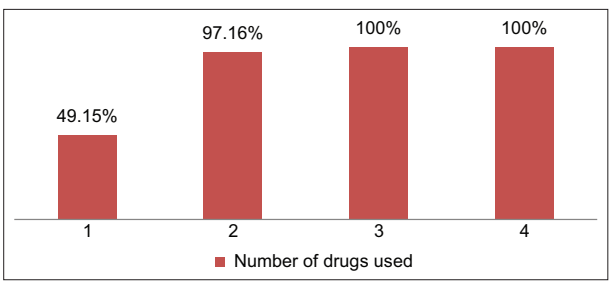

Figure 3: Association of incidence of side effects with number of drugs used

Out of 154 patients, 137 (88.96%) patients used drugs with BAK, out of which 55 (41%) patients required concomitant use of lubricant to overcome dry eyes. Out of 17 (11.03%) patients who used drugs without BAK, only 2 (11%) patients needed an additional use of a lubricant agent. *P*-value was 0.022261, with significance at $P < 0.05$.

Out of 308 eyes, in 274 eyes which were exposed to drugs containing BAK, TBUT values were normal, marginal, and low in, respectively, 95 (34%), 143 (52%), and 36 (14%) eyes. In 34 eyes, which were unexposed to BAK, TBUT values were normal in 29 (85%), and marginal in 5 (15%) eyes. In no eye a low value of TBUT was found. Out of 308 eyes, in 274 eyes which were exposed to drugs with BAK, value of Schirmer's test type 2 was normal and positive in, respectively, 91 (33%) and 183 (67%) eyes. In 34 eyes which were unexposed to drugs without BAK, the values were normal and positive in, respectively, 30 (88%) and 4 (12%) eyes. No eye showed a strongly positive value of Schirmer's test.

The *P*-value with both TBUT and Schirmer's results was <0.00001, with significance at $P < 0.1$ [Figures 4 and 5].

Table 3 shows the association of different anti-glaucoma therapy combinations (monotherapy and polytherapy) with their side effects and corresponding incidences. The most common side effects noted were redness and dryness with incidences in 175 (56.81%) and 169 (54.87%) eyes, respectively [Table 3].

Table 1: Association of duration of anti-glaucoma therapy with values of TBUT (n=308)[a]

Duration of anti-glaucoma drugs in years	TBUT Grading	Number of eyes (%)
0–5 (n=172 eyes)	Normal	108 (62.79)
	Marginal	62 (36.04)
	Low	2 (1.16)
6–10 (n=106 eyes)	Normal	16 (15.09)
	Marginal	79 (74.52)
	Low	11 (10.37)
11–15 (n=16 eyes)	Normal	0 (0)
	Marginal	4 (25)
	Low	12 (75)
16–20 (n=10 eyes)	Normal	0 (0)
	Marginal	2 (20)
	Low	8 (80)
21–25 (n=4 eyes)	Normal	0 (0)
	Marginal	1 (25)
	Low	3 (75)

[a]P<0.00001, the result being significant at P<0.01

Out of 154 patients, 141 (91.55%) patients did not have any systemic side effects showing that anti-glaucoma drugs are generally systemically safe drugs. Metallic taste was seen in 6 (3.89%) patients who used carbonic anhydrase inhibitors in their regimen. Breathlessness was observed in 6 (3.89%) patients using timolol which emphasizes the role of proper elicitation of history and clinical examination before prescribing the drug. Headache was observed in one patient using pilocarpine and fatigue was noted in one patient using a combination of timolol and dorzolamide.

Out of 25 patients who required change in therapy due to unbearable side effects, six patients were on timolol and their indication of change was breathlessness. Travoprost was culprit in three patients with anterior uveitis and cystoid macular edema being the indications. Pilocarpine caused iris pigment epithelial cyst, browache, blurred vision, and headache for which it was changed in two patients. Dorzolamide had to be substituted in three patients due to redness, burning sensation, eye pain, and allergic blepharoconjunctivitis. Follicular conjunctivitis and allergic blepharoconjunctivitis were seen in nine patients in whom brimonidine was being used. Bimatoprost caused redness and burning sensation in two patients where it had to be replaced.

Appropriate therapy had been given for resolution of side effects wherever required. In all the patients, the side effects resolved completely after change of the topical therapy.

Easily acceptable anti-glaucoma therapies were in 80 eyes (26%) which included mainly mono therapy. Therapies with poor tolerance included drugs such as pilocarpine, bimatoprost, and brimonidine and also included eyes which were on multiple drugs. In 190 eyes (61.68%), therapies were coined as moderately acceptable while in 34 eyes (11%), as acceptable with difficulty. Four therapies were not acceptable at all and all of them included pilocarpine and prostaglandin analog in common, making them the main culprits of intolerance. This may be attributable to pro-inflammatory characteristics of both drugs [Table 4].

In our study, no patient required emergency care for any side effect, neither did any patient suffer from any serious adverse events. This suggests that all topical anti-glaucoma drugs are relatively safe in terms of life-threatening side effects especially when used after ruling out all contraindications by proper history taking and thorough clinical examination.

Table 2: Association of duration of anti-glaucoma therapy with values of type 2 Schirmer's, TBUT value[b]

Duration of anti-glaucoma drugs in years	Schirmer's test type 2 grading	Number of eyes (%)
0–5 (*n*=172 eyes)	Normal	100 (58.13)
	Positive	72 (41.86)
	Strongly positive	0 (0)
6–10 (*n*=106 eyes)	Normal	21 (19.81)
	Positive	85 (80.18)
	Strongly positive	0 (0)
11–15 (*n*=16 eyes)	Normal	0 (0)
	Positive	16 (100)
	Strongly positive	0 (0)
16–20 (*n*=10 eyes)	Normal	0 (0)
	Positive	10 (100)
	Strongly positive	0 (0)
21–25 (*n*=4 eyes)	Normal	0 (0)
	Positive	4 (100)
	Strongly positive	0 (0)

[b]The $P<0.00001$, the result being significant at $P<0.01$

Discussion

Medical management by eye drops has always been the mainstay of glaucoma management due to its convenience, safety, and cost-effectiveness compared to other therapeutic modalities but these drug molecules and preservatives used in the eye drops exert some side effects on ocular surface and rarely systematic adverse reactions are also seen in clinical practice.

Preservatives are usually used due to their antimicrobial properties and to increase the stability of the topical formulations.

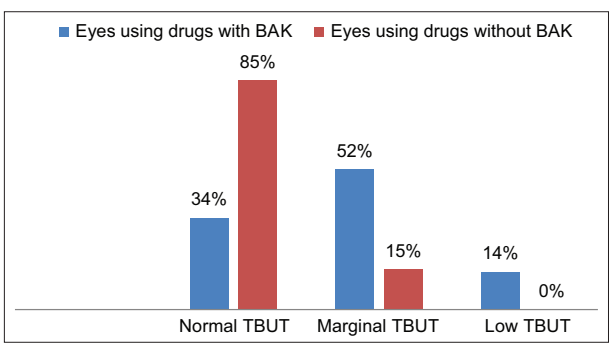

Figure 4: Association of values of TBUT with use of anti-glaucoma drugs with/without BAK (*n*=308)[c]. c: The *P*-value with TBUT's results were <0.00001, with significance at $P<0.1$

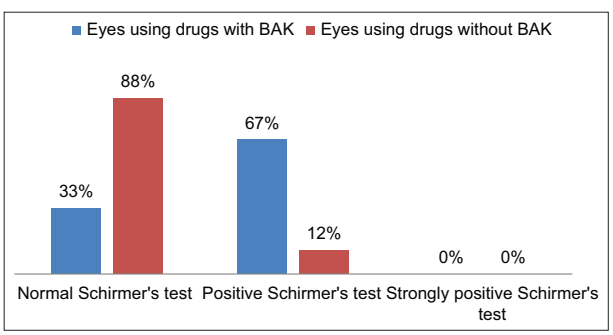

Figure 5: Association of values of Schirmer's test type 2 with use of anti-glaucoma drugs with/without BAK (*n*=308)[d]. d: The *P*-value with Schirmer's results were <0.00001, with significance at $P<0.1$

Table 3: Incidence and type of local side effects (*n*=308)

Drugs	Number of eyes	Side effects (%)											
		None	Dryness	Redness	Burning sensation	Blurred vision	Itching	Browache	Lengthened eyelashes	Periocular hyperpigmentation	Deepening of superior sulcus	Iris heterochromia	Eye pain
Timolol	49	31 (63)	18 (37)	No	No	No	No	No	No	No	No	No	No
Betaxolol	4	No	4 (100)	No	No	No	No	No	No	No	No	No	No
Brimonidine	9	No	No	9 (100)	4 (44.44)	No	No	No	No	No	No	No	No
Travoprost	24	5 (21)	No	8 (33.33)	4 (16.66)	No	No	No	16 (66.66)	9 (37.50)	No	1 (4.16)	No
Latanoprost	24	20 (83.33)	No	No	No	No	No	No	4 (16.66)	No	No	No	No
Bimatoprost	4	No	No	4 (100)	4 (100)	No	No	No	4 (100)	4 (100)	4 (100)	No	No
Brinzolamide	4	4 (100)	No	No	No	No	No	No	No	No	No	No	No
Timolol+Brimonidine	66	No	44 (83.33)	60 (91)	29 (44)	3 (4.54)	3 (4.54)	No	No	No	No	No	No
Timolol+Travoprost	15	No	14 (93.33)	6 (40)	No	No	No	No	10 (66.66)	10 (66.66)	4 (26.66)	1 (6.66)	No
Timolol+Latanoprost	3	No	3 (100)	No	No	No	No	No	No	1 (33.33)	No	No	No
Timolol+Brinzolamide	1	1 (100)	No	No	No	No	No	No	No	No	No	No	No
Timolol+Dorzolamide	10	No	8 (80)	2 (20)	2 (20)	No	No	No	No	No	No	No	No
Brimonidine+Travoprost	5	No	No	5 (100)	2 (40)	No	No	No	1 (20)	No	1 (20)	No	No
Brimonidine+Latanoprost	2	No	No	2 (100)	No	No	No	No	2 (100)	No	No	No	No
Brimonidine+Brinzolamide	2	No	No	2 (100)	2 (100)	No	No	No	No	No	No	No	No
Latanoprost+Brinzolamide	2	2 (100)	No	No	No	No	No	No	No	No	Nono	No	No
Timolol+Brimonidine +Travoprost	17	No	16 (94.11)	13 (76.47)	6 (35.29)	No	No	No	14 (82.35)	6 (35.29)	7 (41.17)	3 (17.64)	No
Timolol+Brimonidine +Latanoprost	13	No	12 (92.93)	13 (100)	4 (30.76)	1 (7.69)	No	No	9 (69.23)	2 (15.38)	2 (15.38)	No	No
Timolol+rimonidine +Dorzolamide	22	No	22 (100)	22 (100)	22 (100)	2 (9)	No	No	No	No	No	No	2 (9)
Timolol+Travoprost +Dorzolamide	2	No	2 (100)	No	2 (100)	No	No	No	No	No	No	No	No
Timolol+Latanoprost +Dorzolamide	4	No	4 (100)	4 (100)	4 (100)	No	No	No	4 (100)	No	No	No	No
Timolol+Brimonidine +Brinzolamide	3	No	2 (66.66)	3 (100)	1 (33.33)	No	No	No	No	No	No	No	No
Timolol+Travoprost +Brinzolamide	1	No	No	No	No	No	No	No	1 (100)	No	No	No	No
Timolol+Travoprost +Pilocarpine	2	No	2 (100)	2 (100)	2 (100)	2 (100)	2 (100)	2 (100)	2 (100)	No	No	No	No

(Contd...)

Table 3: *(Continued)*

Drugs	Number of eyes	Side effects (%)										
		None	Dryness	Redness	Burning sensation	Blurred vision	Itching	Browache	Lengthened eyelashes	Periocular hyperpigmentation	Deepening of superior sulcus	Iris heterochromia	Eye pain
Brimonidine+Latanoprost +dorzolamide	2	No	No	2 (100)	2 (100)	No	No	No	No	No	No	No	No
Timolol+Latanoprost +Pilocarpine	2	No	2 (100)	2 (100)	2 (100)	2 (100)	No	2 (100)	No	No	2 (100)	No	No
Timolol+Brimonidine +Travoprost+Dorzolamide	4	No	4 (100)	4 (100)	4 (100)	No	No	No	4 (100)	No	2 (50)	No	No
Timolol+Brimonidine +Latanoprost+orzolamide	10	No	10 (100)	10 (100)	10 (100)	No	No	No	8 (80)	No	4 (40)	No	No
Timolol+Brimonidine +Travoprost+Pilocarpine	2	No	2 (100)	2 (100)	2 (100)	2 (100)	No	2 (100)	2 (100)	No	No	No	No
Total	308	63	169	175	108	12	5	4	81	32	26	5	2

Various preservatives available in the market are BAK, cetrimide, polyquaternium-1, thiomersal or thimerosal, stabilized oxychloro complex, stabilized chlorite peroxide, chlorhexidin, chlorobutanol, phenylethanol, and methylparaben. Many of them, especially BAK can cause deleterious effects on chronic use through lipid layer and mucus layer alterations producing instability of tear film, increased evaporation of tear film, increased osmolarity of tears, and decreased density of goblet cells, contributing to dry eyes.[8] BAK toxicity has been identified in a number of epidemiologic studies conducted in glaucoma patients receiving topical therapy.[10-15] Different drug molecules themselves can also exert side effects due to their intrinsic characteristics. Timolol affects the corneal and conjunctival epithelium adversely and increases number of fibroblasts and other inflammatory cells causing dry eye. Dorzolamide eye drop formulation has an acidic pH which increases its ocular penetration but, on the other hand, causes intense burning and stinging on instillation. Pilocarpine and prostaglandin analogs are pro-inflammatory and therefore conjunctival hyperemia is a very common association with them. Topical brimonidine as well as all prostaglandin analogues alter the expression of matrix metalloproteinases and their inhibitors in corneal cells and thus contribute to ocular surface disease.[6-8]

In our study, the incidence of side effects was found exceptionally high in female gender. This may correlate perhaps with the more psychologically sensitive nature characteristic of the female gender. We also found 100% incidence of side effects when more than two groups of anti-glaucoma drugs were used simultaneously which signifies that tolerability decreases as the number of medications increase and hence the importance of keeping the number of anti-glaucoma drugs to a minimum has to be borne in mind while treating any patient of glaucoma.

In studies done by Levrat *et al*., discomfort or pain on instillation, symptoms of ocular irritation, and conjunctival signs on ocular examination were more common in patients using preservative-added eye drops than in those using preservative-free drops.[15,16] Ocular surface disease improved significantly among 678 patients who were switched from preservative-added to preservative-free glaucoma medications in a prospective, double-masked, randomized controlled, and 12-week trial.[17] In our study, also we found similar results. In group using eye drops without BAK, concomitant use of lubricant was required in only two patients whereas 55 patients required lubrication in case of use of BAK containing eye drops. In eyes using BAK free eye drops incidence of dry eye was in only 15% eyes whereas in eyes using BAK containing eye drops it was 66%.

A study conducted to determine whether initiation of timolol eye drops was associated with an increased risk of hospitalization for bradycardia enrolled 6,373 patients with at least one hospitalization for bradycardia during the study period; of these 267 patients were exposed to timolol.[18] Another case report was presented where an elderly patient was admitted in intensive care unit due to systemic adverse effects of timolol.[19] In our study, out of 25 patients in whom anti-glaucoma drug had to be changed due to their side effects, six patients were using timolol

Table 4: Acceptability of anti-glaucoma drugs (*n*=308)

Level of acceptance	Number of patients (%)	Drug(s)	Number of patients (%)
Easily accepted	80 (26)	Timolol	31 (38.75)
		Latanoprost	24 (30)
		Travoprost	11 (13.75)
		Brinzolamide	4 (5)
		Timolol+Brimonidine	4 (5)
		Timolol+Travoprost	2 (2.5)
		Timolol+Brinzolamide	1 (1.25)
		Latanoprost+Brinzolamide	2 (2.5)
		Timolol+Travoprost+Brinzolamide	1 (1.25)
Moderately acceptable	190 (61.68)	Timolol	18 (9.47)
		Betaxolol	4 (2.10)
		Brimonidine	7 (3.68)
		Travoprost	7 (3.68)
		Timolol+Brimonidine	48 (25.26)
		Timolol+Travoprost	9 (4.73)
		Timolol+Latanoprost	3 (1.57)
		Timolol+Dorzolamide	10 (5.26)
		Brimonidine+Brinzolamide	2 (1.05)
		Latanoprost+Brimonidine	2 (1.05)
		Travoprost+Brimonidine	4 (2.10)
		Timolol+Brimonidine+Travoprost	14 (7.36
		Timolol+Latanoprost+Brimonidine	11 (5.78)
		Timolol+Latanoprost+Dorzolamide	4 (2.10)
		Timolol+Brimonidine+Dorzolamide	18 (9.47)
		Timolol+Brimonidine+Brinzolamide	3 (1.57)
		Timolol+Latanoprost+Brimonidine	12 (6.31)
		Latanoprost+Brimonidine+Dorzolamide	2 (1.05)
		Timolol+Latanoprost+Brimonidine+Dorzolamide	8 (4.21)
		Timolol+Travoprost+Brimonidine+Dorzolamide	4 (2.10)
Acceptable with difficulty	34 (11)	Brimonidine	2 (5.88)
		Travoprost	6 (17.6)
		Bimatoprost	4 (11.7)
		Timolol+Brimonidine	7 (20.5)
		Timolol+Travoprost	4 (11.7)
		Brimonidine+Travoprost	1 (2.94)
		Timolol+Brimonidine+Latanoprost	1 (2.94)
		Timolol+Brimonidine+Dorzolamide	4 (11.7)
		Timolol+Travoprost+Brimonidine	3 (8.82)
		Timolol+Latanoprost+Pilocarpine	2 (5.88)
Not acceptable at all	4 (1.29)	Timolol+Travoprost+Pilocarpine	2 (50)
		Timolol+Travoprost+Brimonidine+Pilocarpine	2 (50)

eye drops and breathlessness was the indication for change in therapy. No serious systemic side effects warranting emergency management was noted. Thus, we can conclude that majority of the anti-glaucoma drugs are systemically extremely safe for use with none to very low incidence of systemic side effects, especially if prior careful history can be elicited and thorough systemic examination performed to rule out contra-indications.

A double-blind study carried out for 2 years on 50 patients with open-angle glaucoma reported that during treatment with timolol, tear production decreased by 10.2%.[20] In our study, timolol monotherapy was used in 49 patients out of whom 18 patients reported dryness. All the four patients using betaxolol also developed dryness. All patients on combination therapy who developed dryness included timolol in their regimen which suggests its definite potential to cause dry eye.

In one report, two different randomized trials comparing travoprost 0.004% to bimatoprost 0.01% reported an increased occurrence of mild-to-moderate ocular hyperemia in the bimatoprost-treated group.[21] The same report mentions study of once daily use of either travoprost or bimatoprost for 6 weeks followed by crossover for 6 weeks. Mild ocular hyperemia was reported in 31% of subjects in the travoprost-treated group versus 39% of subjects treated with bimatoprost. Moderate hyperemia was reported in 2% of subjects treated with bimatoprost but not in the travoprost-treated group. In our study, no significant side effects were experienced in the 20 eyes on latanoprost monotherapy. Four eyes with latanoprost monotherapy developed lengthened eyelashes. Redness, burning sensation, iris heterochromia, lengthened eyelashes, and periocular hyperpigmentation were seen in 8, 4, 1, 16, and 9 eyes, respectively, with travoprost monotherapy. All patients using bimatoprost developed some or the other side effect in form of redness, burning sensation, periocular hyperpigmentation, and lengthened eyelashes or deepening of superior sulcus. Dryness was not associated with any of the prostaglandin analogue monotherapy. In case of combination therapy, in 34 out of 46 eyes receiving travoprost and in 23 out of 29 eyes receiving latanoprost, lengthening of eyelashes was noted. Periocular hyperpigmentation was seen in 16 out of 32 eyes on travoprost and 3 out of 16 eyes on latanoprost in combination therapy. Deepening of superior sulcus was noted in 14 out of 41 eyes on travoprost and 8 out of 25 eyes on latanoprost in case of combination therapy. All other patients using combination therapy who developed iris heterochromia had travoprost in common.

In our study out of 25 patients which required change of drug, two were using bimatoprost which caused cosmetically unacceptable redness and burning sensation and three were using travoprost out of which two patients developed anterior uveitis and one patient developed cystoid macular edema.

In a multicentric, double-masked, randomized, parallel-group, active-controlled comparison clinical trial, 186 subjects instilled 0.2% brimonidine, and 188 received 0.5% timolol maleate twice daily for 12 months.[22] Allergy was seen in 9% of subjects treated with brimonidine and dry mouth was also more common in this group (33.0% vs. 19.4%). Complaints of burning and stinging were more common in the timolol-treated group (41.9%) than in the brimonidine-treated patients (28.1%). Headache, fatigue, and drowsiness were similar in the two groups. In general, the tolerance to both medications was acceptable. In our study, ine eyes were on brimonidine 0.2% monotherapy and all of them developed redness and burning sensation. Redness was seen in 138 out of 148 eyes on brimonidine in combination therapy. Out of all the patients who experienced burning sensation (n = 151), blurred vision (n = 79), and itching (n = 66), brimonidine was being used as an adjuvant in 88 (58.27%), 4 (5.06%), and 3 (4.54%) patients, respectively. Out of 25 patients who required change of therapy, nine patients were using brimonidine, the reason being follicular conjunctivitis in six patients, and allergic blepharoconjunctivitis in three.

In another study, 105 patients were randomized to dorzolamide or acetazolamide, in addition to timolol, for 12 weeks.[23] More patients receiving acetazolamide discontinued due to clinical adverse experiences than patients receiving dorzolamide; 13 versus 1. The prevalence of systemic adverse experiences for the dorzolamide group dropped by 50% by week 12, but remained unchanged for the acetazolamide group. Ocular burning/stinging was more common in the dorzolamide group (21% vs. 0%).

A double-blind, randomized, active controlled, and parallel group study was conducted multinationally at 31 sites, in 241 patients for 3 months to compare topical brinzolamide 1% twice daily with dorzolamide 2% twice daily, each given with timolol 0.5% twice daily.[24] In general, both regimens were well tolerated. However, more patients experienced at least one adverse event with dorzolamide plus timolol (32.8%) as compared with brinzolamide plus timolol (14.7%); also, more patients experienced ocular discomfort (stinging and burning) after dorzolamide plus timolol (13.1%) than after brinzolamide plus timolol (1.7%). A 18-month, multicenter, double-masked, parallel, and controlled study was conducted to establish the long-term safety and efficacy of brinzolamide 1% 2 and 3 times daily. Adverse events were non-serious and resolved without sequel.[25] In our study, when brinzolamide was used as monotherapy no side effects were experienced by the patients. Redness was reported in all five eyes having brinzolamide in combination regimen and in 44 out of 52 eyes having dorzolamide in regimen. Burning sensation was reported in four out of five eyes on brinzolamide and in 46 out of 54 eyes on dorzolamide. Blurred vision was noted in two out of 22 eyes on dorzolamide. Regarding acceptance of therapy, out of 80 eyes in which therapies were easily accepted, four were on brinzolamide monotherapy whereas no dorzolamide containing regimen was coined as easily acceptable either as monotherapy or in combination. Three patients using dorzolamide required change of drug out of which one patient developed allergic blepharoconjunctivitis, other two developed redness, burning sensation, and ocular pain. Six patients developed metallic taste following usage of topical carbonic anhydrase inhibitors and one patient complained of fatigue after its use.

In a review study of miotics done by Zimmerman *et al.* and Rengstorff *et al.*, a variety of ocular and systemic adverse reactions were confirmed and various ways to avoid them were explored.[26,27] The systemic side effects could be best minimized through proper use of the medication and nasolacrimal occlusion. In our study, total six combination regimens included pilocarpine eye drops and all caused dryness, redness, burning sensation, blurred vision and brow ache, whereas two regimens additionally caused itching and one regimen caused headache. Out of six regimens having pilocarpine, four were termed as not at all acceptable. Two out of 25 patients who changed their therapy due to intolerance were using pilocarpine as part of their regimen, out of which one patient had developed iris pigment epithelial cyst and on the other hand had developed unbearable headache and blurred vision.

In our study, we did not study drug molecules with different concentrations and preservatives individually though our study results can fairly be extrapolated in clinical scenarios with drug concentrations different than standard concentrations. We also did not study influence of these adverse effects of anti-glaucoma drugs on the quality of life and compliance of patients separately, but clearly they are affected detrimentally especially due to cumulative side effects of multiple drugs when used for a long time.

Conclusion

Medical therapy forms a core component of the glaucoma management spectrum. Success of the therapy depends significantly on its tolerability, cost, and compliance. Tolerability and compliance are in turn dependent on comfort in using the drugs which are decided by various preservatives added, stability of the formulation, osmolarity, and pH of the solution and the drug molecule itself. In general, topical anti-glaucoma drugs are very safe with minimal local and systematic side effects with excellent overall tolerability. In majority patients, they cause dryness, burning sensation, and redness which are usually acceptable by most patients. Serious adverse events requiring urgent management are extremely rare. The incidence of side effects increases with increasing age of the patients, increased duration of the therapy, and increasing number of medications. Although few, these side effects can affect the quality of life of the patient and hence the compliance, which can be a limiting factor for the success of the treatment. It is essential, therefore, that the treatment should be tailored individually, monitored regularly and revised when necessary, after thorough history and clinical examination, to minimize the side effects and maximize the outcome of the therapy.

Clinical Significance

Knowing various possible side effects of topical anti-glaucoma medications can help us plan and change therapy to make it suitable for individual patient who, in turn, increases their quality of life and overall satisfaction.

References

1. Quigley HA, Broman A. The number of persons with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol 2006;90:151-6.
2. Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, *et al*. Global data on visual impairment in the year 2002. Bull World Health Organ 2004;82:844-51.
3. Gonzalez P. Glaucoma epidemiology and worldwide health. J Glaucoma 2007;18:124.
4. George R, Ve RS, Vijaya L. Glaucoma in India: Estimated burden of disease. J Glaucoma 2010;19:391-7.
5. Tielsch JM, Sommer A, Katz J, Royall RM, Quigley HA, Javitt J. Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore eye survey. JAMA 1991;266:369-74.
6. Allingham RR, Shields BM, Freedman S. Shield Textbook of Glaucoma. United States: Lippincott Williams and Wilkins 6th ed. 2011.
7. Kanski JJ. Glaucoma, Clinical Ophthalmology a Systemic Approach. 8th ed. Netherlands: Butterworth & Heinmann Elsevier Saunders; 2011. p. 372-439.
8. Stamper RL, Lieberman MF, Drake MV, Becker B. Becker-Shaffer's Diagnosis and Therapy of the Glaucomas. 8th ed. United States: Mosby; 2009.
9. Li N, Deng XG, He MF. Comparison of the Schirmer I test with and without topical anesthesia for diagnosing dry eye. Int J Ophthalmol 2012;5:478-81.
10. Pisella PJ, Pouliquen P, Baudouin C. Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. Br J Ophthalmol 2002;86:418-23.
11. Jaenen N, Baudouin C, Pouliquen P, Manni G, Figueiredo A, Zeyen T. Ocular symptoms and signs with preserved and preservative-free glaucoma medications. Eur J Ophthalmol 2007;17:341-9.
12. Bron A, Chiambaretta F, Pouliquen P, Rigal D, Rouland JF. Efficacy and safety of substituting a twice-daily regimen of timolol with a single daily instillation of nonpreserved beta-blocker in patients with chronic glaucoma or ocular hypertension. J Fr Ophtalmol 2003;26:668-74.
13. Rouland JF. Acceptability of preservative-free beta-blocker eye drops in the treatment of glaucoma. Réflexions Ophtalmol 2011;150:43-6.
14. Van Went C, Brasnu E, Hamard P, Baudouin C, Labbé A. The influence of ocular surface diseases in the management of glaucoma. J Fr Ophtalmol 2011;34:230-7.
15. Levrat F, Pisella PJ, Baudouin C. Clinical tolerance of anti-glaucoma eyedrops with and without a preservative. Results of an unpublished survey in Europe. J Fr Ophtalmol 1999;22:186-91.
16. Thygesen J. Glaucoma therapy: Preservative-free for all? Clin Ophthalmol 2018;12:707-17.
17. 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. Clin Ophthalmol 2010;4:1253-61.
18. Pratt NL, Ramsay EN, Ellett LM, Nguyen TA, Roughead EE. Association between ophthalmic timolol and hospitalisation for bradycardia. J Ophthalmol 2015;2015:567387.
19. Rana MA, Mady AF, Rehman BA, Alharthy A, Huwait B, Riaz A, *et al*. From eye drops to ICU, a case report of three side effects of ophthalmic timolol maleate in the same patient. Case Rep Crit Care 2015;2015:714919.

20. Merté HJ, Merkle W. Results of long-term treatment of glaucoma with timolol ophthalmic solution. Klin Monbl Augenheilkd 1980;177:562-71.
21. Johnstone MA. Hypertrichosis and increased pigmentation ofeyelashes and adjacent hair in the region of the ipsilateral eyelids of patients treated with unilateral topical latanoprost. Am J Ophthalmol 1997;124:554-7.
22. Schuman JS, Horwitz B, Choplin NT, David R, Albracht D, Chen K. A 1-year study of brimonidine twice daily in glaucoma and ocularhypertension. A controlled, randomized, multicenter clinical trial. Chronic Brimonidine Study Group. Arch Ophthalmol 1997;115:847-52.
23. Hutzelmann JE, Polis AB, Michael AJ, Adamsons IA. A comparisonof the efficacy and tolerability of dorzolamide and acetazolamide asadjunctive therapy to timolol. Oral to Topical CAI Study Group. Acta Ophthalmol Scand 1998;76:717-22.
24. Michaud JE, Friren B, International Brinzolamide Adjunctive Study Group. Comparison of topical brinzolamide 1% and dorzolamide 2%eye drops given twice daily in addition to timolol 0.5% in patients with primary open-angle glaucoma or ocular hypertension. Am J Ophthalmol 2001;132:235-43.
25. March WF, Ochsner KI. The long-term safety and efficacy of brinzolamide 1.0% (Azopt) in patients with primary open-angleglaucoma or ocular hypertension. The brinzolamide long-term therapy study group. Am J Ophthalmol 2000;129:136-43.
26. Zimmerman TJ, Wheeler TM. Miotics: Side effects and ways to avoid them. Ophthalmology 1982;89:76-80.
27. Rengstorff R, Royston M. Miotic drugs: A review of ocular, visual, and systemic complications. Am J Optom Physiol Opt 1976;53:70-80.

How to cite this article: Bhagat PR, Trivedi KY. Evaluation and comparison of the safety profile of topical anti-glaucoma drugs in patients of primary open angle glaucoma or ocular hypertension or normal tension glaucoma. Cli Exp Vis Eye Res J 2020;3(2):17-29.

ANNEXURE

PRO FORMA

Preliminary Data

Name:
Age/Sex:
Occupation:
Type of glaucoma: POAG/OHT/NTG
K/C/O glaucoma since:
Using glaucoma medication since:
Medications:
Currently
In past, if any other
Preservative if present
Has there been a change in therapy ever? Yes/No/Don't know
Has there been a change in therapy in recent 6 months? Yes/No/Don't know
Indication for change of therapy:
Better control of disease: Yes/No/Don't know
To overcome side effect of drug: Yes/No/Don't know
If Yes for side effect,
Which side effect?
H/O improvement in symptoms after change of drug
H/O new symptom after change of drug
Any other medication being used
(With indication)
Currently
In past, if any other
Was it added to overcome side effect of drug: Yes/No/Don't know
H/O
Known allergies
Dry eye
Other eye disease
Foreign body
Trauma
H/O eye surgeries
Systemic illnesses
BCVA

SIDE EFFECTS EXPERIENCED BY PATIENTS

Local

Eyepain
Redness
Foreign body sensation
Stinging/burning sensation
Dryness of eyes
Browache
Watering
Discharge
Type
Amount

(Mild/moderate/severe)
(Only at canthus/covering whole lid margin)
Color
More in particular time of day
Consistency
Colored halos
Decreased visual acuity
Blurring of vision
Change in prescription of glasses
Periocular skin
Swelling
Hyperpigmentation
Excoriation
Dryness
Eyelid
Swelling
Redness
Change in contour
Eyelash
Lengthening
Thickening
Hyperpigmentation
Loss
Change in color of eyes/iris

SYSTEMIC

Allergy/anaphylactic Reaction
Skin
Rash
Excoriation
(Site)
Headache
Mild/moderate/severe
Frequency
Site
Association with any other complaints
Association with aura
Time of day
Type
Nausea
Vomiting
Sleep disease
Hallucination
Confusion
Depression
Decreased/loss of attentiveness
Weakness/malaise
Fatigue
Myalgia
Decreased exercise tolerance
Dizziness
Sudden blackouts on waking up
Breathlessness
Chronicity or aggravation of cough/cold/fever

(Mild/moderate/severe)
Any exacerbation OR new detection of cardiovascular morbidity
Dryness of mouth
Decreased appetite
Bitter taste
Hyperacidity
GIT upset
Urinary frequency
Tingling sensation of angles of mouth/fingers and toes

CLINICAL EXAMINATION

Findings on torch light examination
Findings on slit lamp examination
Tests for dry eye
TBUT
Schirmer's test
Without lignocaine
With lignocaine

H/O EMERGENCY THERAPY FOR SIDE EFFECT

Needed/Not needed
Diagnosis/Don't know
Outcome of therapy
No improvement
Mild improvement
Significant improvement
Resolved completely
Post emergency therapy
Continued same molecule
(Concentration/dose/frequency)
Changed to molecule of same drug class
Changed drug class
Stopped medical therapy (Alternative therapy prescribed)

ACCEPTANCE OF THE DRUG

Easily acceptable
Moderately acceptable
Acceptable with difficulty
Not acceptable at all