

Prevalence of Ocular Surface Disease in Patients with Glaucoma using Topical Antiglaucoma Medications

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Abstract

Purpose: To establish the prevalence of ocular surface disease (OSD) in glaucoma patients using topical intraocular pressure-lowering (IOP) therapy and to compare the frequency and severity of symptoms with the control group of normal subjects.

Methods: This prospective, multicenter, observational study included patients with glaucoma in four different Departments of Ophthalmology. A matched group of normal subjects served as controls. For each patient we have collected detailed family history, clinical records and calculated ocular surface disease index (OSDI) scores (0-100), based on the information obtained from OSDI questionnaires.

Results: In total, we have evaluated 160 patients. Of those, 110 were glaucoma patients and 50 were normal subjects. Among 110 glaucoma treated patients 83 (75%) had OSDI scores indicating mild to severe OSD. Among 50 patients without glaucoma 15 (30%) had OSDI score indicating mostly mild to moderate OSD. The severity of symptoms correlates with the number of IOP medications used and the duration of treatment.

Conclusion: This study confirms the high prevalence of OSD in patients treated for glaucoma with topical IOP medications. The adverse effect of these agents can influence the compliance and successful treatment of glaucoma patients.

Keywords: Antiglaucoma medications; BAK; Glaucoma; Ocular surface disease; Prevalence

Introduction

Ocular surface disease (OSD) can be defined as a group of disorders that affects various components of the ocular surface. It is a very common disorder in clinical practice and one of the most frequent reasons of patients' visits to ophthalmologists. It is basically described as condition that in different ways affects the stability and function of the tear film [1]. Causes of OSD are environmental and genetic factors, age, dry eye syndrome, blepharitis and meibomian gland dysfunction as well as preservative-containing eye drops. Patients with OSD usually present with general discomfort, itching, dryness, redness of the eye, burning sensation, foreign body sensation, visual disturbance, difficulty in reading or working in front of a computer and photophobia. Glaucoma is optic nerve neuropathy and one of the leading cause of blindness among elderly patients [2,3]. Even though we have developed laser trabeculoplasty and filtration surgical treatments most of our patients are using topical antiglaucoma drops for years, usually more than one medication on daily basis, to maintain good intraocular pressure (IOP) values. Majority of glaucoma medications contain some level of benzalkonium chloride (BAK) which is used to decrease the risk of contamination or to enhance their permeability. Numerous studies suggest that frequent and long-term

instillation of preserved ophthalmic products may compromise ocular surface and induce symptoms such as dryness, irritation or negative impact on visual function [4-6].

We have to keep in mind that glaucoma is a chronic disease and most of our patients will need lifetime treatment. Therefore healthy ocular surface improves patient's comfort and lowers the risk of failed glaucoma filtering surgery in the future [7]. Previously conducted studies that similarly used the Ocular surface disease index (OSDI) questionnaire showed that 40% to 59% of glaucoma patients also have OSD [8,9]. The purpose of the current study was to investigate the prevalence of OSD among our glaucoma patients using topical IOP - lowering therapy. We also wanted to compare the frequency and severity of symptoms with the control group of healthy subjects without glaucoma.

Materials and Methods

This was a prospective, multicenter; observational study approved by the Independent Ethics Committee of each individual study site and was conducted in accordance with the tenets of the Declaration of Helsinki. Our study included 160 eyes: 110 with glaucoma and 50 of normal subjects examined between September 2011 and March 2012 in four different Ophthalmology Departments in Croatia and Bosnia and Herzegovina (two in Zagreb, one in Split and one in Mostar).

Informed consent was obtained from each participant before enrolment. Eligible patients were at least 30 years of age. Glaucoma participants included patients with primary open-angle glaucoma (POAG) who had IOP adequately controlled using one or more glaucoma medication. All medications used in this study were preserved with BAK. POAG participants had glaucomatous optic nerve head cupping and glaucomatous visual field defects in at least 2 consecutive examinations. The group of healthy participants included individuals with no history of glaucoma or frequent usage of intraocular drops, no presence or history of blepharitis within the previous year, no prior corneal surgery, no history of ocular inflammatory disease e.g. Herpes simplex keratitis, best-corrected visual acuity according to Snellen charts of 0.5, IOP <21 mmHg, normal optic nerve head appearance and normal visual field testing results. Healthy eyes served as the control group and they were age - matched and sex-matched to the patients with glaucoma.

Exclusion criteria in glaucoma group were previous intraocular surgery or trauma, any ocular laser surgery within the previous six months, any contact lens wear within 30 days before enrolment, visual acuity with their usual correction less than 0,5 according to Snellen, current use of topical corticosteroids, artificial tears, topical non-steroid anti-inflammatory drugs or cyclosporine ophthalmic emulsion like Restasis or current use of punctual plugs, suspected or diagnosed Sjögren's syndrome or rheumatic/autoimmune disorder like rheumatoid arthritis, systemic lupus erythematosus or scleroderma. All patients were asked to complete OSDI questionnaire. OSDI questionnaire was developed by Allergan Inc. Outcome Research Group (Irvine CA) to provide a rapid assessment of the severity of symptoms of OSD and their impact on vision related function [10].

The questionnaire consists of 12 questions concerning symptoms and problems associated with dry eye. The questions are divided into three groups regarding patients experience with ocular symptoms, vision- related functioning and environmental triggers. Patients were asked to indicate whether they experienced any of the symptoms or problems on the list in the previous week, and if so, how often. Questions include sensitivity to light, grittiness of the eyes, soreness of the eyes, blurred vision, poor vision; whether they experienced limitations with reading, driving at night, watching television, or working with a computer; and whether their eyes felt uncomfortable in windy conditions, very dry places or in air conditioned places [11,12]. The 12 items of the OSDI questionnaire were graded on a 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 of the time. Total OSDI score was calculated for each patient based on the following formula-

sum of scores of all questions answered × 25 / total number of questions answered

Patients were assessed on a scale of 0-100 with higher scores representing greater disability. Patients were grouped into 4 categories by OSDI score: normal (scores 0-12), mild OSD symptoms (13-22), moderate OSD symptoms (23-32), severe OSD symptoms (33-100) [13]. Patients' medical records were used to obtain medical history including detailed data on the use of medication and duration of therapy. We used this information to divide patients into groups according to number of medications used and duration of therapy. Statistical analysis for severity distribution of OSDI scores among two groups was made using chi-square test. Differences in the number of OSDI scores with respect to the number of drugs used and the duration of therapy were tested by Kruskal Wallis test. A P value of 0.05 or less was considered to be statistically significant. Statistical

analyses were performed using the SPSS 15.0 package (SPSS Inc., Chicago, IL).

Results

One hundred and sixty patients from four different Ophthalmology Departments participated in this study by completing OSDI questionnaire. Of those 110 were open-angle glaucoma patients, and 50 were healthy subjects. The mean SD ± age of the participants who completed the study was 72 ± 6 years, ranging from 37-92 years. In glaucoma group 50 (45%) patients were males and in control group 22 (44%).

Figure 1 shows the distribution of OSDI scores in glaucoma patients and in the control group. Among 110 glaucoma treated patients 83 (75%) had OSDI scores indicating mild to severe OSD compared to 15 (30%) in the control group. Figure 2 shows the most frequent complaints of glaucoma patients using hypotensive therapy. They most often included sensitivity to light, poor vision and discomfort in windy conditions.

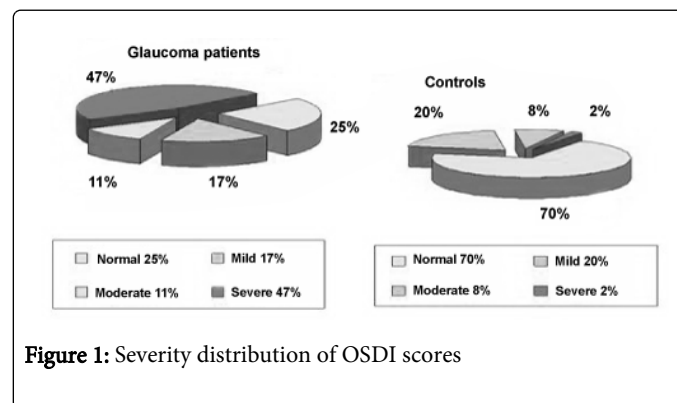


Figure 1: Severity distribution of OSDI scores

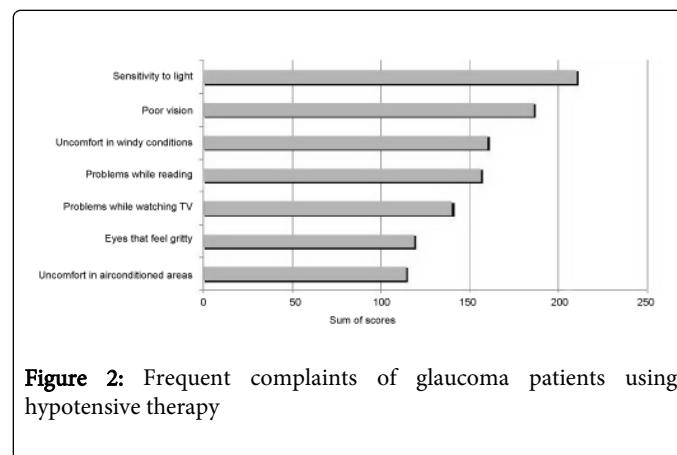


Figure 2: Frequent complaints of glaucoma patients using hypotensive therapy

Figure 3 shows OSDI scores in patients on 1, 2, or 3 or more medications. 65 (59,09%) patients were using 1 antiglaucoma medication, 35 (31.8%) patients were using 2 antiglaucoma eye drops, and 10 (9.1%) patients were using 3 or more antiglaucoma eye drops. OSDI scores differed among patients using different numbers of medications (P=0.048). Patients on a single eye drop had a median OSDI score of 22,7 (0-87,5), those who were on 2 eye drops had 35,0 (2,1-70) and on three eye drops 44,1 (14,6-72,5). Median OSDI score raises gradually from 20.1 in those that were treated less than 1 year up to 36.2 in those that are treated 5-7 years, and then again slightly falls

up to 34.2 in those that receive therapy for more than 10 years (Figure 4; $P=0.042$).

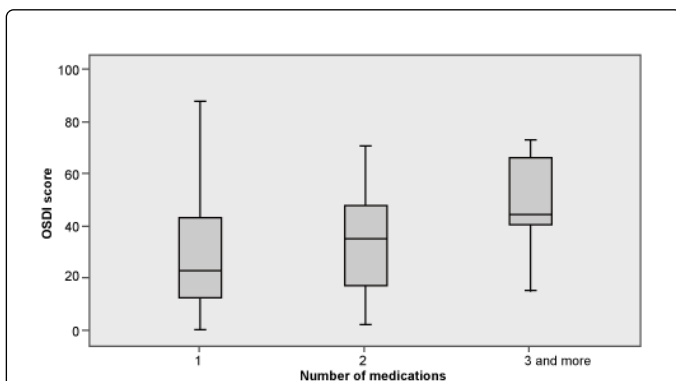


Figure 3: OSDI scores in patients on 1, 2 or 3 or more antiglucoma medications

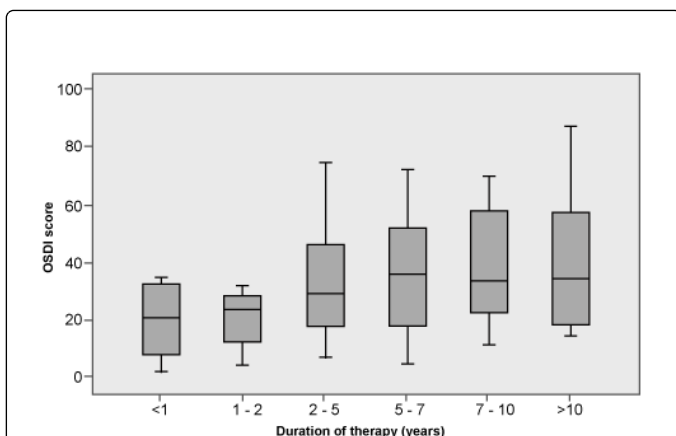


Figure 4: OSDI score in relation to the duration of therapy

Discussion

In this study we have observed a high prevalence of OSD symptoms in patients treated for glaucoma - 3/4 (75%) of glaucoma patients on hypotensive medications have symptoms of OSD. Of those, 17% had scores in accordance with mild OSD, 11% with moderate OSD and 47% with severe OSD. Our results show that glaucoma patients were twice as likely to experience OSD symptoms, compared to control group without glaucoma. Local antiglucoma therapy, which patients use every day for many years, may compromise the ocular surface. The impact of OSD on quality of life is best shown by the utility study performed by Schiffman et al. [14] who demonstrated how patients viewed their dry eye disease in terms of quality of life compared with angina pectoris. The study found that patients with severe OSD were in the same range in terms of quality of life as those with severe angina. The impact of OSD on visual function is also important. Miljanovic et al. [15] showed that crucial daily activities of modern living such as reading, computer use, professional work, driving and watching television are all negatively impacted by OSD.

In this multicentre study 110 glaucoma patients and 50 control subjects completed the OSDI survey. The OSDI is a valid and reliable instrument for measuring the severity of dry eye disease, and it possesses the necessary psychometric properties to be used as an end point in clinical trials as proved by several clinical studies [10].

Fechtner et al. [8] also used OSDI to describe the prevalence of OSD among glaucoma treated patients. In their study which enrolled 630 glaucoma patients, 48.4% of the patients reported mild to severe symptoms which is significantly less compared to our results in which 3/4 of glaucoma patients had mild to severe OSD (47% with severe OSD). The higher prevalence of OSD in our study may have several explanations. This difference could be explained by the differences in the selection of patients (more severe disease, differences in age, duration of therapy and the type and number of medications used). Patients enrolled in this study are all treated in the specialized glaucoma departments for severe form of disease and most of them have used multiple antiglucoma eye drops for a long time period (70,4% patients were treated for more than 7 years).

Previous studies are showing a strong correlation between the number of IOP-lowering medications used and the presence of dry eye [8,16,17]. Study by Rossi et al. [16] described the prevalence of OSD and they wanted to assess quality of life in subjects with glaucoma. In this study 40% of patients using 2 or 3 antiglucoma medications had symptoms of OSD, which is in line with our findings. Patients on a single medication had the lowest median of OSDI score followed by patients on 2 medications and the highest median was on 3 or more medications. This difference was significant ($P=0.048$) (Figure 3).

In an international study published by Garcia-Feijoo et al. [18], patients who had a glaucoma diagnosis of less than 6 years had a mean OSDI score of 18 units, which is indicative of mild OSD, while patients who had a glaucoma diagnosis of 6 years or longer had a mean OSDI score that was significantly worse ($P=0.03$), indicating moderate OSD. This is in accordance with our findings where OSDI score increases with the duration of glaucoma disease and glaucoma therapy ($P=0.042$) (Figure 4).

Figure 4 also shows that OSDI score tend to slightly fall in patients that are on therapy for >10 years. This can be explained by another factor that may complicate the assessment of OSD using OSDI and it is corneal hypoesthesia. Corneal sensitivity tends to decrease with age but it is also a consequence of long-term effect of preservative-containing antiglucoma eye drops on corneal surface [19,20]. The chronic patients have less innervation of the ocular surface and as a consequence experience less pain and discomfort which can result in slightly better OSDI score.

We found that the OSD symptoms have been reported in 30% of the normal subjects and in up to 75% of glaucoma subjects. Gosh et al. [21] has also found similar results. A significant increase in the prevalence of OSD signs was observed in the glaucoma population, 70.3%, compared to controls, 33% [21]. Studies have demonstrated the possibility that interaction between glaucoma and OSD syndrome increases because of topical ocular medications [5,8,22]. Once applied, any topical medication exerts toxicity on ocular surface from the active compound. The majority of medications used by our patients have varying concentrations of benzalkonium chloride (BAK). Even in low concentrations BAK can trigger apoptosis in human corneal and conjunctival epithelial cells and it can cause chronic stromal inflammation [23-25]. As a detergent, it disrupts the tear film after only a single drop [26] and with the chronic use decreases the density

of goblet cells in the conjunctival epithelium [27] which are producing mucous layer of the tear film. In addition, it has a detergent effect on corneal barrier function by breaking down the intercellular adhesion which makes the tear film unstable and unable to maintain the healthy ocular surface [28]. When patients are using multiple medications there is a cumulative effect of BAK which may explain our finding that OSDI scores increased with the number of IOP-lowering medications used. Leung et al. reported that the use of more BAK-containing eye drops was significantly associated with higher prevalence of abnormal results in lissamine green test [9]. Another study evaluated the efficacy, safety and tolerability of changing to travoprost BAK-free from prior prostaglandin therapy in 691 patients with primary open-angle glaucoma or ocular hypertension. All patients were switched from latanoprost or bimatoprost to BAK-free travoprost for 12 weeks. OSD scores improved from severe to moderate, from moderate to mild and from mild to normal. There was also significant decrease in hyperemia with travoprost BAK-free and equal or better IOP control. As for patient preference, 72% of patients preferred travoprost without BAK [29]. Those results agree with study of Pisella et al. [30] who showed that symptoms and signs of OSD are more prevalent in glaucoma patients using preservative -containing eyedrops compared with patients using preservative -free eyedrops.

Our study included patients from four different Departments in Croatia and Bosnia and Herzegovina in order to avoid selection biases and have the representative sample for our region. To our knowledge this is the first study that established the prevalence of OSD in glaucoma patients using topical IOP therapy in our region. The identical results were reported in different regions of Croatia and Bosnia and Herzegovina in spite of climate and demographic differences (inland and Mediterranean parts). We wanted to compare our results on OSDI score in patients treated for open-angle glaucoma with the published studies from other regions.

Our study has some limitations. Although OSDI questionnaire is written in Croatian, questions 6-9 that concerne visual symptomatology are not objective because patient cannot see because of other ocular pathology, other than OSD symptoms. The OSDI questionnaire is a subjective tool and it would be useful to have an objective clinical test to assess the ocular surface, although the correlation between OSDI scores and severity of clinical presentation has been reported to be poor [9]. Furthermore we have not evaluated the relationship between the type of medication used with OSDI score. Many patients used different types of medications for different periods of time, or were switched from one to another or to multiple medications. Considering this it was difficult to evaluate the relationship between the type of the medication and OSDI score. The most frequent complaints of glaucoma patients using hypotensive therapy in our sample were sensitivity to light, poor vision and discomfort in windy conditions. In conclusion, despite its various limitations, this study shows that OSD is a very serious problem in patients treated for glaucoma. Three quarters of glaucoma patients on hypotensive medications in Croatia and Bosnia and Herzegovina have symptoms of OSD. Severity of symptoms correlated with the number of IOP medications used and duration of hypotensive therapy.

The adverse effects of antiglaucoma medications can influence compliance, success of treatment and can ultimately greatly influence the quality of life of the glaucoma patients. We can provide a better ocular surface for our patients by recommending to avoid environmental circumstances such as dry air, long working hours in front of computer and by switching from BAK preserved medication

to a medication with a smaller percentage of BAK, or BAK free. To verify the beneficial influence of BAC free agents on OSD, further studies that would include comparison of BAK and BAK free agents are needed.

References

1. Kahook MY, Springs CL (2008) Treating ocular surface disease in glaucoma. *Glaucoma Today* 6: 53-56.
2. Pascolini D, Mariotti SP (2012) Global estimates of visual impairment: 2010. *Br J Ophthalmol* 96: 614-618.
3. Quigley HA, Broman AT (2006) The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol* 90: 262-267.
4. Furrer P, Mayer JM, Gurny R (2002) Ocular tolerance of preservatives and alternatives. *Eur J Pharm Biopharm* 53: 263-280.
5. Baudouin C, Labbé A, Liang H, Pauly A, Brignole-Baudouin F (2010) Preservatives in eyedrops: the good, the bad and the ugly. *Prog Retin Eye Res* 29: 312-334.
6. Skalicky SE, Goldberg I, McCluskey P (2012) Ocular surface disease and quality of life in patients with glaucoma. *Am J Ophthalmol* 153: 1-9.
7. Baudouin C (1996) Mechanisms of failure in glaucoma filtering surgery: a consequence of antiglaucomatous drugs? *Int J Clin Pharmacol Res* 16: 29-41.
8. Fechtner RD, Godfrey DG, Budenz D, Stewart JA, Stewart WC, et al. (2010) Prevalence of ocular surface complaints in patients with glaucoma using topical intraocular pressure-lowering medications. *Cornea* 29: 618-621.
9. Leung EW, Medeiros FA, Weinreb RN (2008) Prevalence of ocular surface disease in glaucoma patients. *J Glaucoma* 17: 350-355.
10. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL (2000) Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol* 118: 615-621.
11. Rossi GCM (2011) How to diagnose the ocular surface disease in treated glaucoma patients. *Eur Ophthalmic Rev* 5: 38-42.
12. Ozcura F, Aydin S, Helvacı MR (2007) Ocular surface disease index for the diagnosis of dry eye syndrome. *Ocul Immunol Inflamm* 15: 389-393.
13. Miller KL, Walt JG, Mink DR, Satram-Hoang S, Wilson SE, et al. (2010) Minimal clinically important difference for the ocular surface disease index. *Arch Ophthalmol* 128: 94-101.
14. Schiffman RM, Walt JG, Jacobsen G, Doyle JJ, Lebovics G, et al. (2003) Utility assessment among patients with dry eye disease. *Ophthalmology* 110: 1412-1419.
15. Miljanovic B, Dana R, Sullivan DA, Schaumberg DA (2007) Impact of dry eye syndrome on vision-related quality of life. *Am J Ophthalmol* 143: 409-415.
16. Rossi GC, Tinelli C, Pasinetti GM, Milano G, Bianchi PE (2009) Dry eye syndrome-related quality of life in glaucoma patients. *Eur J Ophthalmol* 19: 572-579.
17. Erb C, Gast U, Schremmer D (2008) German register for glaucoma patients with dry eye. I. Basic outcome with respect to dry eye. *Graefes Arch Clin Exp Ophthalmol* 246: 1593-1601.
18. Garcia-Feijoo J, Sampaolesi JR (2012) A multicenter evaluation of ocular surface disease prevalence in patients with glaucoma. *Clin Ophthalmol* 6: 441-446.
19. Bourcier T, Acosta MC, Borderie V, Borrás F, Gallar J, et al. (2005) Decreased corneal sensitivity in patients with dry eye. *Invest Ophthalmol Vis Sci* 46: 2341-2345.
20. Martone G, Frezzotti P, Tosi GM, Traversi C, Mittica V, et al. (2009) An in vivo confocal microscopy analysis of effects of topical antiglaucoma therapy with preservative on corneal innervation and morphology. *Am J Ophthalmol* 147: 725-735.
21. Ghosh S, O'Hare F, Lamoureux E, Vajpayee RB, Crowston JG (2012) Prevalence of signs and symptoms of ocular surface disease in individuals treated and not treated with glaucoma medication. *Clin Experiment Ophthalmol* 40: 675-681.

22. Rossi GC, Pasinetti GM, Scudeller L, Raimondi M, Lanteri S, et al. (2013) Risk factors to develop ocular surface disease in treated glaucoma or ocular hypertension patients. *Eur J Ophthalmol* 23: 296-302.
23. Pisella PJ, Debbasch C, Hamard P, Creuzot-Garcher C, Rat P, et al. (2004) Conjunctival proinflammatory and proapoptotic effects of latanoprost and preserved and unpreserved timolol: an ex vivo and in vitro study. *Invest Ophthalmol Vis Sci* 45: 1360-1368.
24. Malvitte L, Montange T, Vejux A, Baudouin C, Bron AM, et al. (2007) Measurement of inflammatory cytokines by multicytokine assay in tears of patients with glaucoma topically treated with chronic drugs. *Br J Ophthalmol* 91: 29-32.
25. Baudouin C (1996) Side effects of antiglaucomatous drugs on the ocular surface. *Curr Opin Ophthalmol* 7: 80-86.
26. Baudouin C, de Lunardo C (1998) Short-term comparative study of topical 2% carteolol with and without benzalkonium chloride in healthy volunteers. *Br J Ophthalmol* 82: 39-42.
27. Herreras JM, Pastor JC, Calonge M, Asensio VM (1992) Ocular surface alteration after long-term treatment with an antiglaucomatous drug. *Ophthalmology* 99: 1082-1088.
28. Ishibashi T, Yokoi N, Kinoshita S (2003) Comparison of the short-term effects on the human corneal surface of topical timolol maleate with and without benzalkonium chloride. *J Glaucoma* 12: 486-490.
29. Henry JC, Peace JH, Stewart JA, Stewart WC (2008) Efficacy, safety, and improved tolerability of travoprost BAK-free ophthalmic solution compared with prior prostaglandin therapy. *Clin Ophthalmol* 2: 613-621.
30. Pisella PJ, Pouliquen P, Baudouin C (2002) Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. *Br J Ophthalmol* 86: 418-423.