Prevalence of Ocular Surface Disease in Glaucoma Patients

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Purpose: To examine the prevalence of ocular surface disease (OSD) in glaucoma patients.

Methods: This was a cross-sectional study. One hundred and one patients, 18 years of age or older, with open-angle glaucoma or ocular hypertension were consecutively recruited for the study. Patients with a history of use of cyclosporine, steroids, topical ocular nonsteroidal anti-inflammatory drugs, or punctal plugs within the last 3 months were excluded. Each patient completed an Ocular Surface Disease Index questionnaire and underwent evaluation by Schirmer test, corneal and conjunctival lissamine green staining, and tear break-up time.

Results: Using Ocular Surface Disease Index for measuring symptoms of dry eye, 60 (59%) patients reported symptoms in at least 1 eye. Severe symptoms were reported by 27 (27%) patients. Schirmer testing showed 62 (61%) patients with decrease in tear production in at least 1 eye. Severe tear deficiency was presented in 35 (35%) patients. Corneal and conjunctival lissamine green staining showed positive results in 22 (22%) patients. None had severe staining. Tear break-up time showed abnormal tear quality in 79 (78%) patients and severe decrease in tear quality was found in at least 1 eye in 66 (65%) patients. Multivariate logistic regression models were used to investigate the association between the number of benzalkonium chloride (BAK)-containing eyedrops and results on the clinical tests of OSD. After adjustment for age and sex, each additional BAK-containing eyedrop was associated with an approximately 2 times higher odds of showing abnormal results on the lissamine green staining test (odds ratio = 2.03; 95% confidence interval: 1.06 to 3.89; $P = 0.034$).

Conclusion: A large proportion of patients with open-angle glaucoma or ocular hypertension had signs and/or symptoms of OSD in at least 1 eye. The coexistence of OSD and the use of BAK-containing medications may impact vision-related quality of life in this patient population.

Key Words: glaucoma, ocular surface disease, dry eyes, banzalkonium chloride, ocular hypertension

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Ocular surface disease (OSD) is a leading cause of patient visits to ophthalmologists.[1–6] In the United States, the prevalence of symptomatic OSD is estimated to be 15% among individuals aged 65 years or older.[7] It is characterized by an inadequate quantity of tears, an unstable tear film secondary to poor quality of tears, ocular surface breakdown, and/or symptoms such as irritation, burning, foreign body sensation, dryness, photophobia, fatigue, and fluctuating visual acuity. OSD symptoms can be debilitating and often severe, affecting a patient's quality of life and ability to work.[8]

Several factors are considered to influence the prevalence of OSD, such as age, sex, and race.[9] In addition, OSD is associated often with other ocular diseases, such as meibomian gland dysfunction and blepharitis. Use of preservative-containing eyedrops also has been implicated in the development or worsening of OSD.[10,11] A deleterious effect of benzalkonium chloride (BAK) on the ocular surface has been demonstrated in vitro as well as in vivo in both animals and humans. Preservatives have a detergent effect on the lipid layer of the tear film[12] and also can decrease the density of goblet cells in the conjunctival epithelium.[13] These actions result in a reduction in the stability of the precorneal tear film, compromising its ability to provide protection and trophic factors to the cornea.

Glaucoma patients are presumably at a higher risk for developing OSD, as both diseases are more common in older patients. Further, glaucoma patients are usually treated with preservative-containing pressure-lowering eyedrops that may contribute to OSD. However, there is a paucity of data with regard to the prevalence of OSD in glaucoma patients.

The purpose of the current study was to investigate the prevalence of symptoms and signs of OSD in patients with glaucoma.

METHODS

The study was carried out with the approval of the Institutional Review Board of the University of California, San Diego, in accordance with the requirements of the Code of Federal Regulations on the Protection of Human Subjects, and in accord with the Health Insurance Portability and Accountability Act (HIPPA) regulations. All patients were recruited consecutively during a regular scheduled glaucoma clinic appointment at the Shiley Eye

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Center of the University of California, San Diego, from October 2006 to February 2007.

Inclusion criteria for the study included (1) being 18 years of age or older, of both sexes and all races; (2) signature on the informed consent document; (3) a clinical diagnosis of primary open-angle, pseudoexfoliation, or pigment-dispersion glaucoma, or ocular hypertension in both eyes; and (4) the ability to read and complete the Ocular Surface Disease Index (OSDI) questionnaire written in English (Fig. 1). A diagnosis of glaucoma was established on the basis of the presence of visual field defect (GHT outside normal limits and/or PSD with $P < 5\%$) and/or the presence of signs of glaucomatous optic neuropathy (rim thinning, excavation, and/or retinal nerve fiber layer defects). Patients with ocular hypertension had a history of intraocular pressure of above 22 mm Hg without signs of glaucomatous optic neuropathy or visual field loss. Exclusion criteria included (1) an inability to understand the trial procedures, and thus the inability to give informed consent; (2) current use or use within the last 3 months of Restasis, steroids, or topical ocular nonsteroidal anti-inflammatory drugs; (3) current use of punctal plugs; and (4) previous glaucoma, corneal, or conjunctival surgery.

After providing informed consent, qualified patients were given the OSDI questionnaire (Fig. 1) to complete.[14] Demographic information, a brief medical history, and information on concomitant medicine use, including use of artificial tears, were obtained from the patient's medical records. After completing the OSDI questionnaire, patients underwent 3 standard clinical tests of the ocular surface in the order listed, including Schirmer test (without anesthesia), corneal and conjunctival lissamine green staining, and tear break-up time (TBUT). All the questionnaires and examinations were completed in 1 day.

For the Schirmer test (without anesthesia), the patients were asked to look up and the lower eyelid was drawn gently downward and temporally. The rounded bent end of the sterile strip was hooked in the lower cul-de-sac over the junction of the temporal and central one-third of the lower eyelid margin. The testing period was initiated. To minimize the potential for conjunctival staining from this test, the patients were asked to gently close their eyelids until 5 minutes had elapsed and the strips were removed. As the tear front would continue advancing a few millimeters after it had been removed from the eyes, the tear front was marked with a pencil after 5 minutes. The amount of wetting was measured using the graduated paper scale included in the box of strips. If the tear front had moved unevenly, we measured from the notch to the middle of the diagonal line. Only whole numbers rounding up to the next whole number were recorded if the tear front was at or at greater than the half-millimeter mark. After Schirmer testing, a 25-μL drop of freshly prepared lissamine green was instilled using a micropipette. The drop was gently delivered from the tip of the micropipette to the lower palpebral conjunctiva. 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.[11] Corneal and conjunctival lissamine green staining was evaluated after 30 seconds but before 2 minutes had elapsed after instillation.

Patient Number | Patient Initials | Physician's Name | Date of Visit (Month / Day / Year)

OCULAR SURFACE DISEASE INDEX (OSDI)

Please answer the following questions by checking the box that best represents your answer

	ALL of the time	MOST of the time	HALF of the time	SOME of the time	NONE of the time	NOT applicable
Have you experienced any of the following during the last week:						
1. Eyes that are sensitive to light?	☐	☐	☐	☐	☐	
2. Eyes that feel gritty?	☐	☐	☐	☐	☐	
3. Painful or sore eyes?	☐	☐	☐	☐	☐	
4. Blurred vision?	☐	☐	☐	☐	☐	
5. Poor vision?	☐	☐	☐	☐	☐	
Have problems with your eyes limited you in performing any of the following during the last week:						
6. Reading?	☐	☐	☐	☐	☐	☐
7. Driving at night?	☐	☐	☐	☐	☐	☐
8. Working with a computer or bank machine (ATM)?	☐	☐	☐	☐	☐	☐
9. Watching TV?	☐	☐	☐	☐	☐	☐
Have your eyes felt uncomfortable in any of the following situations during the last week:						
10. Windy conditions?	☐	☐	☐	☐	☐	☐
11. Places or areas with low humidity (very dry)?	☐	☐	☐	☐	☐	☐
12. Areas that are air conditioned?	☐	☐	☐	☐	☐	☐

Calculation of OSDI: $\text{OSDI} = \frac{\text{sum of severity for all questions answered}}{4 \times (\text{total number of questions answered})}$

ALL of the time = 4; MOST of the time = 3; HALF of the time = 2; SOME of the time = 1; NONE of the time = 0

NOTE: questions answered N/A for the calculations = a NON answered question

FIGURE 1. Ocular Surface Disease Index questionnaire.

Subsequently, 5 μL of a 2% sodium fluorescein solution was instilled into the inferior cul-de-sac. The drop at the tip of the delivery micropipette was gently touched to the lower palpebral conjunctiva. Examination was performed with the slit lamp at 10 times magnification and TBUT was measured over the cornea using cobalt illumination. Patients were asked to blink normally and the time for tear break-up was measured only up to 10 seconds.

The findings in case of each patient were designated as normal, mild to moderate, or severe for each individual measure. 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.[10] 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. The severity designations used for TBUT were the following: ≥ 10 seconds, normal; 5 to 9 seconds, mild to moderate; and <5 seconds, severe. 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; and 4, all of the time. The total OSDI score was calculated using the following formula: OSDI = [(sum of scores for all questions answered) $\times$ 100]/[(total number of questions answered) $\times$ 4].[10] 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 the following: 0 to 5.9, normal; 6.0 to 14.9, mild to moderate; and ≥ 15.0, severe.[10] The criteria for disease severity were set up a priori for the study.

For each patient, we considered the eye that showed worse results for each specific test. If both the eyes had equally severe results on a particular test, then 1 eye was chosen randomly by the flip of a coin.

A multivariate logistic regression model was used to evaluate the relationship between the use of eyedrops and results on the OSDI questionnaire and clinical tests of OSD. The results of each test were categorized as normal/abnormal and entered as dependent variables. The number of BAK-containing eyedrops was entered. The model was adjusted for age and sex, also entered as independent variables.

RESULTS

One hundred and one patients (202 eyes) participated and completed all the tests involved in the study. Thirty-nine patients were invited to participate in the study, but chose not to participate owing to transportation issues, time limitation, and/or concerns about the study safety. Seventy-nine (78%) patients had a diagnosis of open-angle glaucoma and 22 (22%) patients were diagnosed with ocular hypertension. Forty-six (45%) patients were using 1 eyedrop, 37 (36%) patients were using 2 eyedrops, and 10 (10%) patients were using 3 eyedrops. Eight patients (8%) were not using any topical ocular medication. The mean $\pm$ SD age of the participants who completed the study was 67 ± 12 years, ranging from 36 to 90 years. Sixty-six (65%) patients were males.

Table 1 summarizes the results obtained on the OSDI questionnaire and on the 3 clinical tests. The overall prevalence of OSD varied from 22% to 78%, depending on the specific test evaluated. Using OSDI for measuring symptoms of dry eye, 60 (59%) patients reported symptoms in at least 1 eye. Severe symptoms were reported by 27 (27%) patients. Schirmer testing showed that 62 (61%) patients had at least 1 eye with a decreased tear production. Severe tear deficiency was present in 35 (35%) patients. Corneal and conjunctival lissamine green staining showed positive results in 22 (22%) patients. None had severe staining. TBUT showed abnormal tear quality in 79 (78%) patients and a severe decrease in tear quality was found in at least 1 eye in 66 (65%) patients.

To further analyze the data, we dichotomized the results of the OSDI questionnaire and clinical tests to normal versus abnormal. Results indicating mild to moderate disease as well as severe disease were grouped as abnormal. Figure 2 shows the agreement between the results. Only 11 patients (11%) had abnormal results on all 3 tests. All of these patients also reported symptoms of OSD on the OSDI questionnaire.

Figure 3 shows the relationship between the presence of symptoms as assessed by the OSDI questionnaire and the results of the 3 clinical tests. Patients with OSDI symptoms often had normal testing [Schirmer test (64%), lissamine green staining (58%), and TBUT (55%)]. There was no correlation between the results on these clinical tests and the presence of symptoms of OSD.

We also investigated the relationship between the use of BAK-containing eyedrops and presence of OSD symptoms and signs. Results of multivariate logistic regression models adjusting for age and sex are shown in Table 2. After adjustment for age and sex, each additional BAK-containing eyedrop was associated with an approximately 2 times higher odds of showing abnormal results on the lissamine green staining test (odds ratio = 2.03; 95% confidence interval: 1.06 to 3.89; $P = 0.034$). No relationship was observed between the number of BAK-containing eyedrops and results on the other clinical tests. Figures 4A to D illustrates the relationship between the number of BAK-containing eyedrops used and the results on the OSDI questionnaire and OSD clinical tests.

TABLE 1. Number (%) of Patients With Each Result on the OSDI, Schirmer Test, Lissamine Green Staining, and TBUT

Test Results	OSDI	Schirmer Test	Lissamine Green Staining	TBUT
Normal	41 (41%)	39 (39%)	79 (78%)	22 (22%)
Mild/moderate	33 (33%)	27 (27%)	22 (22%)	13 (13%)
Severe	27 (27%)	35 (35%)	0 (0%)	66 (65%)

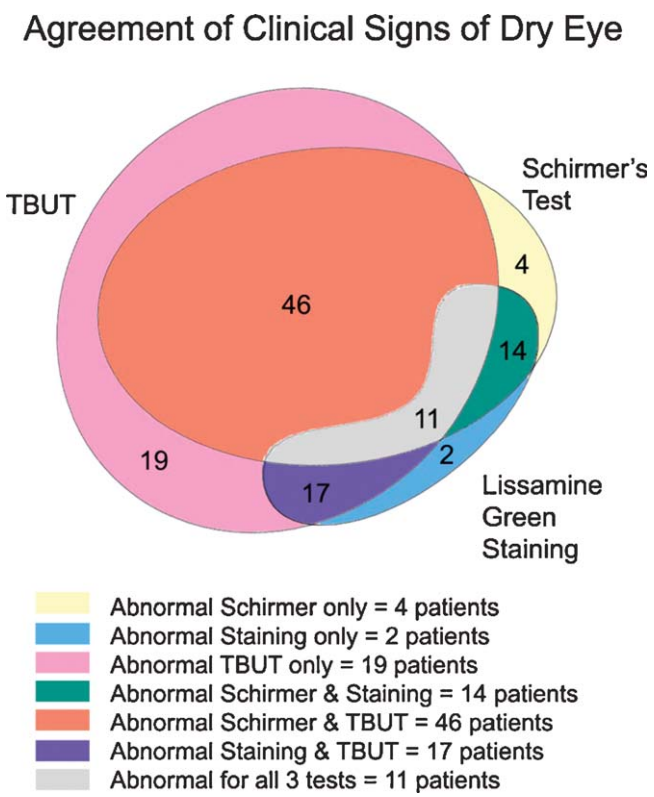

FIGURE 2. Agreement on the results obtained by the 3 clinical tests for diagnosing signs of dry eye disease.

DISCUSSION

A high prevalence of symptoms and signs of OSD were found in a population of patients with glaucoma or ocular hypertension. There is a lack of widely accepted criteria for diagnosing OSD. Several studies have relied only on reports of symptoms to diagnose the condition. The OSDI questionnaire was designed as a screening survey to assess symptoms and their impact on vision-related functions.[14] This questionnaire has been reported to have excellent test-retest reliability and to effectively discriminate between normal, mild to moderate, and severe OSD as defined by both the physician's assessment of severity and a composite disease-severity score. Moreover, the OSDI has been demonstrated to have good sensitivity and specificity in distinguishing between normal subjects and patients with OSD.[14] In our study, 59% of the patients reported symptoms of dry eye and severe symptomatology was reported by 27% of the overall group of patients. Although a high prevalence of OSD symptoms was reported by our patients, the correlation with results of the other OSD clinical tests was poor. A large proportion of patients who reported symptoms on the OSDI questionnaire had normal results on the clinical tests. Conversely, a significant proportion of patients with abnormal results on the OSD clinical tests had normal results on the OSDI questionnaire. This is in agreement with previous studies that have also found a poor correlation between objective and subjective signs of dry eye disease.[15,16]

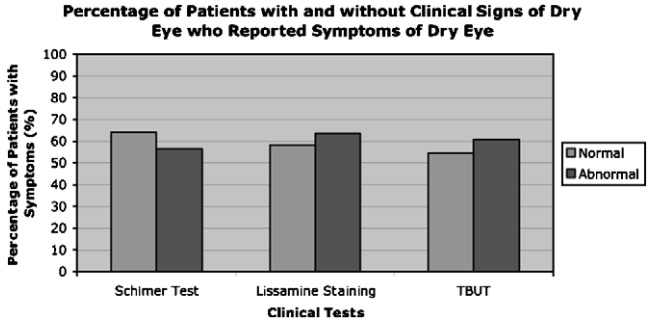

FIGURE 3. Relationship between the presence of symptoms as assessed by the Ocular Surface Disease Index questionnaire and the results of the Schirmer, lissamine green staining, and tear break-up time tests.

In view of the difficulties in diagnosing OSD in prevalence studies, the use of a test battery of measurements has been suggested to include the use of a validated questionnaire of symptoms, as well as tests to demonstrate ocular surface damage, tear instability, and tear hyperosmolarity. If a combination of positive symptoms on the OSDI questionnaire and at least one abnormal OSD clinical test was used to diagnose OSD in our population, the prevalence figures would be 14%, 35%, or 48% depending on the clinical test used (lissamine green staining, Schirmer test, or TBUT, respectively).

The prevalence figures of OSD in our study are higher than those reported in population-based prevalence studies. The Melbourne Visual Impairment Project (MVIP) examined the prevalence of OSD in 926 patients aged 40 years and older.[17] OSD was diagnosed in 10.8% by rose Bengal staining, 16.3% by Schirmer test, 8.6% by TBUT, 7.4% with 2 or more signs of the condition, and 5.5% with any severe symptom. In the Salisbury population-based survey, 14.6% of the 2520 residents examined reported one or more symptoms of OSD often or all of the time.[5,18] In the Beaver Dam Eye Study (BDES) cohort of 3722 patients aged from 48 to 91 years, the prevalence of OSD by self-reported history was found to be 14.4%.[7] In a large study conducted in the United States, involving almost 40,000 women, the age-adjusted prevalence of OSD was 9.8% in women older than 75 years.[1]

The higher prevalence of OSD in our study has several possible explanations. We evaluated a specific population of clinic-based glaucoma patients within a tertiary referral practice. These patients may have more severe glaucoma and consequently may be treated with multiple preservative-containing eyedrops. Also, it is possible that some of these patients were even referred owing to OSD symptoms or signs. Whatever the explanations may be, our study demonstrates a high prevalence of OSD. It is important to emphasize, however, that our results may not be extrapolated to unselected populations of patients with glaucoma, and

TABLE 2. Results of Multivariate Logistic Regression Models for the Association Between Abnormal Results on the OSDI Questionnaire and on the Clinical Tests of Dry Eye Disease

Variable	OSDI Odds Ratio (95% CI)	Schirmer Test Odds Ratio (95% CI)	Lissamine Green Staining Odds Ratio (95% CI)	TBUT Odds Ratio (95% CI)
Number of BAK-containing eyedrops (per additional medication)	1.42 (0.84 to 2.41)	0.81 (0.49 to 1.35)	2.03 (1.06 to 3.89)	0.60 (0.32 to 1.14)
Age (per year)	1.06 (0.75 to 1.81)	1.26 (0.89 to 1.79)	1.29 (0.80 to 2.09)	1.24 (0.82 to 1.89)
Sex (female)	0.82 (0.35 to 1.91)	0.52 (0.22 to 1.23)	3.92 (1.41 to 10.92)	2.86 (0.86 to 9.47)

A multivariate model was constructed for each test (OSDI, Schirmer test, lissamine green staining, TBUT), using the result of the test (abnormal versus normal) as the dependent variable, and the number of BAK-containing eyedrops, age, and sex as independent variables.
CI indicates confidence interval.

future studies should investigate OSD prevalence in this situation.

In our study, we also investigated the relationship between the use of BAK-containing eyedrops and OSD symptoms and signs. A deleterious effect of BAK has been demonstrated both in vitro as well as in vivo.[11] A concentration of 0.007% of BAK induces a lysis of 50% of cultured epithelial cells in less than 2 minutes.[19] Numerous reports have demonstrated that prolonged use of topical ocular medications preserved with BAK may exacerbate symptoms and signs associated with OSD and have adverse effects on the conjunctiva and cornea. These effects include the induction of subclinical inflammation, reduction of corneal epithelial barrier function, destabilization of the tear film, and an overall higher incidence of patient complaints of dryness and irritation in users of BAK-containing eyedrops.[11] BAK exerts its damaging action mainly through a direct cytotoxic mechanism, accentuated by the cumulative effect of repeated administrations of preserved eyedrops.[20] In our study, we found that the use of more BAK-containing eyedrops was significantly associated with a higher prevalence of abnormal results on the lissamine green test. In other words, patients using more BAK-containing eyedrops had more staining of their corneal/conjunctival surfaces, indicating the presence of OSD, even after adjustment for age and sex. Such a positive relationship was not observed for the other OSD clinical tests. This may be due to the lack of specificity of the Schirmer test and TBUT for diagnosing OSD. Our results agree with those of Pisella et al[21] showing that symptoms and signs of OSD are more prevalent in glaucoma patients using preservative-containing eyedrops compared with patients using preservative-free eyedrops. It is important to note, however, that the cross-sectional design of our study does not allow one to state conclusively that the use of BAK-containing eyedrops is the cause of OSD in our patients.

Our study has limitations. We were not able to evaluate the relationship between the type of medication and duration of therapy with clinical signs and symptoms

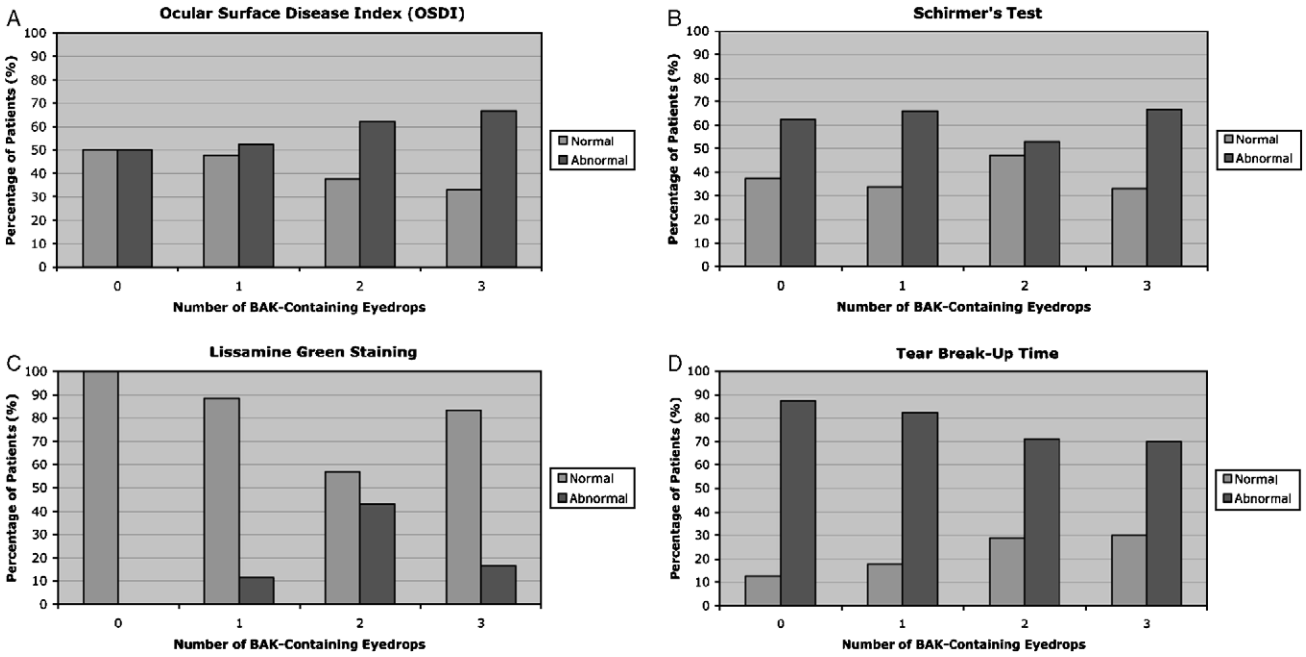

FIGURE 4. Relationship between the number of benzalkonium chloride-containing eyedrops and the results of the Ocular Surface Disease Index questionnaire (A), Schirmer test (B), lissamine green staining (C), and tear break-up time (D).

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