ORIGINAL ARTICLE

Topical glaucoma therapy and ocular surface disease: a prospective, controlled cohort study

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ABSTRACT • RÉSUMÉ

Objective: To evaluate the association between the intensity and duration of glaucoma topical therapy and severity of signs and symptoms of ocular surface disease (OSD).

Design: Single-site, prospective, controlled, cross-sectional study.

Participants: Sixty-one patients with no diagnosis of or previous treatment for OSD were identified.

Methods: Patients were assigned to 2 groups: the glaucoma group with 31 patients diagnosed with primary open-angle glaucoma and using at least 1 topical intraocular pressure (IOP)–lowering medication and the control group including 30 patients with no diagnosis of glaucoma or history of topical therapy usage. The right eye of each patient was arbitrarily chosen. Each patient completed an Ocular Surface Disease Index (OSDI) questionnaire and underwent evaluation of the ocular surface by conjunctival and corneal lissamine green (LG) staining and tear breakup time (TBUT). The intensity index (drops/wk × therapy duration in years) was calculated to quantify the topical therapy.

Results: OSDI scores of the glaucoma group correlated to the intensity index ($r = 0.46$, CI 0.13–0.69). The glaucoma group had a higher mean OSDI score than the control group (18.97 ± 9.5 versus 6.25 ± 5.7, $p = 5.85E-08$). Abnormal TBUT and LG staining scores were prevalent in the glaucoma group compared with the control group (68% vs 17%, $p = 0.000078$; 65% vs 3%, $p = 2.9$ E-07).

Conclusions: Patients on glaucoma therapy have a greater prevalence of OSD symptoms, and their intensity index correlates to the OSDI score. The intensity index reflects quantitatively the amount of treatment and can be further validated in future studies as a predicting tool for OSD development.

Objet : Évaluer le rapport entre l'intensité ainsi que la durée d'un traitement topique du glaucome et la gravité des signes et des symptômes de maladie de la surface oculaire (MSO).

Nature : Étude transversale, contrôlée et prospective à site unique.

Participants : 61 patients sans diagnostic ni traitement antérieur de MSO.

Méthodes : Nous avons formé deux groupes : un groupe de 31 patients qui avaient reçu un diagnostic de glaucome primaire à angle ouvert et qui utilisaient au moins un agent de réduction de la pression intraoculaire (PIO), et un groupe contrôle formé de 30 patients sans diagnostic de glaucome ni antécédents d'utilisation de médicaments topiques. Nous avons choisi arbitrairement l'œil droit de chaque patient. Chaque patient a répondu au questionnaire *Ocular Surface Disease Index* (indice de maladie de la surface oculaire ou IMSO) et a subi deux formes d'évaluation de la surface oculaire : une coloration au vert Lissamine de la conjonctive et de la cornée et un test du temps de rupture du film lacrymal (TRFL). Nous avons calculé l'indice d'intensité (gouttes/semaine x durée du traitement en années) pour quantifier le traitement topique.

Résultats : Il y avait corrélation entre les scores IMSO des patients atteints de glaucome et l'indice d'intensité ($r = 0,46$, IC = 0,13–0,69). Le score IMSO moyen de ce groupe dépassait celui du groupe contrôle (18,97 ± 9,5 contre 6,25 ± 5,7, valeur p = 5,85 E-08). Il y avait une plus forte proportion de scores anormaux pour le TRFL et la coloration au vert Lissamine dans le groupe de patients avec glaucome que dans le groupe contrôle (68 % contre 17 %, valeur $p = 0,000078$; 65 % contre 3 %, valeur $p = 2,9$ E-07).

Conclusion : Les patients traités pour glaucome ont une prévalence supérieure de symptômes de MSO, et il y a corrélation entre leur indice d'intensité et le score IMSO. L'indice d'intensité reflète quantitativement le traitement topique. Des études ultérieures pourraient valider la valeur de cet indice comme outil prédictif du développement de MSO.

Ocular surface disease (OSD) is a common comorbidity in patients with glaucoma.[1,2] OSD, which consists of a spectrum of diseases including keratitis dry eye, conjunctivitis, and lid disease,[3] plays an important role in treatment adherence[4] and patient's quality of life.[5] In 1 report, nearly half of medically treated patients with glaucoma reported OSD symptoms.[6] OSD has been found to be aggravated by topical intraocular pressure (IOP)–lowering medication usage.[7,8] The preservative benzalkonium chloride has been traditionally incriminated in the ocular toxicity associated with IOP-lowering medications,[9] although recent studies have raised suspicion around other preservatives.[10,11] Moreover, OSD symptoms appear to be correlated with the number of ocular hypotensive medications.[6] In a recent study, OSD management resulted in

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Presented in part at the Association for Vision in Research and Ophthalmology in Fort Lauderdale, Fla., May 2, 2011, and the Association for Vision in Research and Ophthalmology in Fort Lauderdale, Fla., May 6, 2012.

Originally received May 17, 2014. Final revision Oct. 24, 2014. Accepted Nov. 7, 2014

Can J Ophthalmol 2015;50:132–136

http://dx.doi.org/10.1016/j.jcjo.2014.11.006

improved IOP control, suggesting that optimizing the ocular surface may help in the control of IOP.[12] The significant overlap between the 2 conditions suggests an association between the 2 diseases. However, there is a paucity of data on the temporal relation between OSD symptoms and the intensity of topical IOP-lowering medication usage.

In this study, we examined patients without prior diagnosis of or treatment for OSD for early signs and symptoms of OSD depending on their usage of IOP-lowering medications. We also defined an intensity index that will allow the clinician to quantify the duration and intensity of topical therapy. Similar to the concept of a tobacco "pack-year," this intensity index will provide clinicians with a metric with which to evaluate a patient's past and future risk for development of OSD. Our study aims at evaluating the association between this newly defined intensity index and the Ocular Surface Disease Index (OSDI), tear breakup time (TBUT), and lissamine green (LG) staining. We also examined the prevalence of OSD in patients using IOP-lowering medications.

Methods

This was a single-site, cross-sectional study conducted at the Institute of Ophthalmology and Visual Science at Rutgers New Jersey Medical School, in accordance with the requirements of the Code of Federal Regulations on the Protection of Human Subjects and the Health Insurance Portability and Accountability Act and with the approval of the Institutional Review Board. The study adhered to the tenets of the Declaration of Helsinki. The study was approved by the Institutional Review Board of the Institute of Ophthalmology and Visual Science at Rutgers New Jersey Medical School.

In total, 61 patients were recruited and assigned to 2 groups: the glaucoma group with 31 patients diagnosed with primary open-angle glaucoma (POAG) and using at least 1 topical IOP-lowering medication, and the control group including 30 patients with no diagnosis of glaucoma or history of topical therapy or IOP-lowering medications. Subjects were recruited during a regularly scheduled clinic visit from October 2010 to September 2011. Informed consent was obtained from all participants. For all patients, the right eye was arbitrarily selected as the study eye. Inclusion criteria for the study included: (*i*) being at least 18 years of age from both sexes and all ethnic backgrounds, and (*ii*) the ability to read and complete the OSDI questionnaire written in English. The glaucoma study group included an additional inclusion criterion: (*iii*) the current use of at least 1 topical IOP-lowering medication for POAG. Exclusion criteria for both groups included: (*i*) a prior diagnosis of or treatment for OSD, (*ii*) the use of punctual plugs or artificial tears, (*iii*) the use of any nonglaucoma topical therapy, and (*iv*) ocular surgery within the past 3 years. The control group had additional exclusion criteria: (*v*) the use of any glaucoma topical therapy, and (*vi*) the use of artificial tears.

Qualified patients were enrolled in either the glaucoma or the control study group according to the earlier inclusion and exclusion criteria and were then given the OSDI questionnaire to complete. OSDI was designed in 1997 by the Outcomes Research Group at Allergan Inc (Irvine, Calif.).[13] It consists of a 12-item questionnaire that provides a subjective assessment of the visual symptoms associated with dry eye syndrome in a clinical setting and covers 3 domains: ocular symptoms, vision-related function and environmental triggers.[13] The OSDI has been validated in English-speaking subjects[13] and scored on a scale from 0 to 100 using the following formula: (Sum of scores for all questions answered) × 25 / total number of questions answered. Based on their OSDI score, subjects were grouped into 2 categories: normal (scores of 0–12) and abnormal (13–100).[14] Detailed medical history, demographic information, and concomitant medication history were collected. A detailed ocular medication history was then obtained from the patient and his or her medical records. The duration of ocular hypotensive drops usage was obtained, and this information was verified by reviewing the patients' pharmacy records. If such information was not available, the patient was not enrolled in the study. The duration of glaucoma therapy (number of weeks), the total number of applied drops (number of drops/eye), and the intensity index (number of drops per week × therapy duration in years) were noted.

The patients subsequently underwent a comprehensive ophthalmic examination and 2 standardized clinical tests of the ocular surface: corneal and conjunctival LG staining and TBUT measurement. Both the questionnaire and the examination were completed during a single office visit. TBUT and LG score readers were masked to OSDI scores. TBUT was evaluated by using 5 μL preservative-free 2% sodium fluorescein solution, placed in the lower conjunctival cul-de-sac of each eye using a fixed volume micropipette. Examination was performed with the slit lamp at 10 times magnification, and TBUT was measured using the cobalt illumination. After being asked to blink twice, the time for tear breakup was measured in each eye, up to 10 seconds. A breakup time $\leq$10 seconds was recorded as abnormal, and a TBUT longer than 10 seconds was recorded as normal. Corneal and conjunctival LG staining were evaluated between 30 seconds and 2 minutes after installation of a fixed micropipette volume of 25 μL preservative-free LG dye in the lower conjunctival cul-de-sac. The TBUT and LG staining evaluations were all performed by the same investigator for consistency. Although the investigator was not masked to whether the subject was in the glaucoma or control groups, the investigator had no access to the subject's OSDI score. The Oxford grading system was used to assess the LG staining, with 0-I recorded as normal and II-V recorded as abnormal.[15]