Comparative Analysis of Ocular Redness Score Evaluated Automatically in Glaucoma Patients Under Different Topical Medications

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Giuseppe Giannaccare, MD, PhD, FEBOphth,[1] Marco Pellegrini, MD,[2] Federico Bernabei, MD,[2] Carlotta Senni, MD,[2] Maria Aloi, MD,[1] Giovanna Carnovale Scalzo MD,[1] Domenico Ceravolo, CO,[1] Claudio Iovino, MD,[3] Vincenzo Scorcia, MD.[1]

[1] *Department of Ophthalmology, University Magna Græcia of Catanzaro, Catanzaro, Italy*

[2] *Ophthalmology Unit, S.Orsola-Malpighi University Hospital, Bologna, Italy*

[3]*Eye Clinic, Multidisciplinary Department of Medical, Surgical and Dental Sciences, Second University of Naples, Naples, Italy*

Corresponding Author

Giuseppe Giannaccare

Professor of Ophthalmology

Department of Ophthalmology, University Magna Græcia of Catanzaro

Viale Europa, 88100, Germaneto (Catanzaro), Italy

Mobile: 0039 3317186201

Phone: 0039 09613647041

Fax: 0039 09613647094

ORCID iD: 0000-0003-2617-0289

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Abstract

Purpose: To compare ocular redness score calculated automatically between glaucoma patients and healthy controls, and to assess the associations between this score and both demographical and clinical characteristics.

Methods: Glaucoma patients under different topical medications and matched controls were enrolled in this observational cross-sectional study. The Keratograph 5M (Oculus Optikgeräte GmbH) was used to automatically measure 5 redness scores: global; nasal bulbar; temporal bulbar; nasal limbal; temporal limbal. The Student t and ANOVA tests were used to compare continuous variables between groups. A multiple linear regression analysis was performed to evaluate the associations between redness scores and the use of different active principles.

Results: One hundred two glaucoma patients and 32 controls were included. Ocular redness scores were significantly higher in glaucoma patients compared to controls (always $P<0.001$). The number of active principles was significantly associated with all the redness scores (always $P<0.05$). The use of carbonic anhydrase inhibitors (CAIs) was the strongest predictor of overall redness, followed by prostaglandin analogues (PAs) and alpha-adrenergic agonists (AAAs) (respectively, $\beta=0.400$, $P=0.002$; $\beta=0.330$, $P=0.013$; $\beta=0.311$, $P=0.044$). The post hoc analysis measuring the effect of different PAs on redness scores showed that overall redness and bulbar nasal redness scores were significantly lower in patients using tafluprost and latanoprost compared to those using travoprost and bimatoprost 0.01% (respectively, $P=0.025$ and $P=0.024$).

Conclusion: Ocular redness was significantly higher in patients with glaucoma compared to control subjects. The number of active principles and the use of PAs, CAIs and AAAs were associated with higher redness scores.

Key Words

Glaucoma; Ocular redness; Hyperemia; Conjunctival redness; Glaucoma medications.

Introduction

Conjunctival redness or hyperemia is one of the most common ocular responses to insults of various origin and can be present in different ocular diseases such as conjunctivitis, dry eye, allergy, infection and contact lens wearing [1–3]. Moreover, conjunctival hyperemia is a common side effect of certain eye drops applied chronically to the ocular surface, and in particular of topical anti-glaucoma medications. This adverse reaction can either result from the main agent or from preservatives used in the drug vehicle. In patients with glaucoma, conjunctival hyperemia is not only a cosmetic problem but may also reduce patient's adherence to therapy thus facilitating disease progression. Previous reports that tried to address the clinical significance of conjunctival redness by analyzing specimens from biopsy found that signs of inflammation were present only in a small not significant number of samples; conversely, in the majority of cases it was caused by a non-inflammatory vascular congestion [4, 5].

Traditionally, conjunctival hyperemia is evaluated with subjective ordinal scales that are subject to intrinsic subjectivity with a degree of inter-observer and/or intra-observer variation, thus suffering from poor reproducibility [6–8]. To overcome these limitations, various systems based on digital image analysis have been developed, with good results in term of sensitivity and repeatability [8–11]. Among these, Oculus Keratograph 5M (Oculus Optikgeräte GmbH, Wetzlar, Germany), a commercially available corneal topographer with a built-in color camera, permits the automatic measurement of conjunctival hyperemia. Previous studies have already validated the reliability of Keratograph 5M for the evaluation of conjunctival hyperemia [12–14].

The purpose of this study was to compare conjunctival hyperemia in glaucoma patients under topical medications and healthy controls by means of Keratograph 5M, and to further assess the associations between redness score and both demographical and clinical variables.

Methods

Study Design and Patients

This observational cross-sectional study was conducted at the Department of Ophthalmology of the University Magna Græcia of Catanzaro (Italy) between January 2019 and September 2019. The study was performed in accordance with the principles of the Declaration of Helsinki, and was approved by the local Institutional Review Board. Fully written informed consent was obtained for all included patients. Consecutive patients with primary open angle glaucoma (POAG) under topical intraocular pressure (IOP)-lowering medications were screened for enrollment. Healthy sex- and age-matched subjects who came to our Center for routine annual eye examinations were included as a control group. Exclusion criteria for both groups were any type of secondary glaucoma, history of ocular surgery (with the exception of cataract surgery at least six months before study enrollment), contact lens wearing, any usage of eye drops, including tear substitutes, within 1 month before the evaluation, apart for glaucoma medications and any pre-existing ocular surface disease, including dry eye disease, history of chemical and thermal burns, pinguecula, pterygium and nevus. Demographical and clinical data including the number and type of active principles, treatment duration, presence/absence and type of preservatives were recorded.

Oculus Keratograph 5M

All measurements were performed by a masked investigator (D.C.) using the Oculus Keratograph 5M Topographer (Oculus Optikgeräte GmbH) in a room with ambient lighting. All the examinations were performed approximately at the same time of the day, at least 3 hours following the last instillation of eye drops. The patients were asked to focus on the fixation mark, so the entire corneal area appears in the center of the image. After acquisition of an anterior segment photograph, the system automatically generates 5 redness scores (global, nasal bulbar, temporal bulbar, nasal limbal

and temporal limbal), which are based on ratio between blood vessels and the rest of the analyzed bulbar conjunctiva [12]. Tear meniscus height (TMH) was measured manually using the caliper provided by the system. If both eyes met the inclusion criteria, only the right one was analyzed. For each parameter, three measurements were taken, and the average was considered for the statistical analysis.

Statistical Analysis

SPSS statistical software (SPSS Inc, Chicago, IL) was used for data analysis. Values are expressed as mean ± standard deviation. The Shapiro-Wilk's test was used to assess normality of data. The Student t test was used to compare continuous variables between the glaucoma group and the control one. In the glaucoma group, the Student t-test was used to compare mean redness scores between males and females; patients using and not using prostaglandin analogues (PAs), carbonic anhydrase inhibitors (CAIs), alpha-adrenergic agonists (AAAs), beta-blockers preservatives; patients on preservative free glaucoma eye drops and those using glaucoma eye drops with different types of preservatives. The ANOVA test was used to compare mean redness scores between patients using 1, 2, 3 and 4 active principles. Pearson correlation analysis was used to assess the correlations between redness scores and continuous variables. A multiple linear regression analysis including the use of the different active principles eye drops was performed with a forward stepwise selection method. A value $P < 0.05$ was considered statistically significant.

Results

A total of 102 patients with glaucoma and 32 control subjects were included in the study. Mean age was 69.0 ± 10.4 years in the glaucoma group and 64.4 ± 6.7 years in the control group ($P = 0.221$). All the ocular redness scores were significantly higher in the glaucoma group compared to the control one (always $P < 0.001$) (Table 1).

Figure 1 shows the representative images of ocular redness from a control subject (Part A) and 2 glaucoma patients using different medications (Parts B and C).

The comparison of mean redness scores between patients with different clinical characteristics in the glaucoma group are reported in Table 2. Males showed a significantly higher overall, bulbar nasal and bulbar temporal redness scores (respectively, $P = 0.006$; $P = 0.007$; $P = 0.043$). The number of active principles was significantly associated with all the redness scores (always $P < 0.05$). Patients under treatment with PAs showed a significantly higher bulbar nasal and limbal nasal redness scores (respectively, $P = 0.044$; $P = 0.020$). The use of CAIs and AAAs was associated with a higher value of all the redness scores (always $P < 0.05$). Age was significantly correlated with overall redness score (R = 0.201; $P = 0.043$), bulbar temporal (R = 0.221; $P = 0.025$), limbal nasal (R = 0.343; $P < 0.001$) and limbal temporal (R = 0.219; $P = 0.027$). Treatment duration and TMH showed no significant correlations with redness scores (always $P > 0.05$). A post hoc analysis was performed to evaluate the effect on redness scores of different PAs. Overall redness and bulbar nasal redness scores were significantly lower in patients using tafluprost and latanoprost compared to those using travoprost and bimatoprost 0.01% (respectively, 1.76 ± 0.62 vs 2.06 ± 0.54, $P = 0.025$; 1.81 ± 0.75 vs 2.17 ± 054, $P = 0.024$). In the glaucoma group, 71 patients used eyedrops containing benzalkonium chloride (BAK), 22 containing Polyquaternium-1, 2 containing other preservatives and 7 used preservative-free eyedrops. The differences of all redness scores between patients using eyedrops containing BAK and Polyquaternium-1 were not significant. In particular, overall, bulbar nasal, bulbar temporal, limbal nasal and limbal temporal redness scores in patients using BAK and

polyquaternium-1 were respectively 1.75 ± 0.59 vs. 1.68 ± 0.56, 1.82 ± 0.67 vs. 1.81 ± 0.77, 1.73 ± 0.58 vs. 1.62 ± 0.53, 1.21 ± 0.59 vs. 1.12 ± 0.57, and 1.26 ± 0.58 vs. 1.18 ± 0.45 (always $P > 0.05$).

The results of multiple regression analysis are reported in Table 3. The R^2 for the overall model to predict overall redness score was 19.0%. The use of CAIs was the strongest predictor of overall redness, followed by PAs and AAAs (respectively, $P = 0.002$; $P = 0.013$; $P = 0.044$). The R^2 for the overall model to predict bulbar nasal redness score was 17.3%. The use of PAs was the strongest predictor of bulbar nasal redness, followed by CAIs and AAAs (respectively, $P = 0.009$; $P = 0.008$; $P = 0.041$). The R^2 for the overall model to predict bulbar temporal redness score was 11.3%. The use of CAIs was the only predictor of bulbar temporal redness ($P = 0.001$). The R^2 for the overall model to predict limbal nasal redness score was 30.5%. The use of AAAs was the strongest predictor of limbal nasal redness, followed by CAIs and PAs (respectively, $P = 0.001$; $P < 0.001$; $P = 0.002$). The R^2 for the overall model to predict limbal temporal redness score was 23.4%. The use of CAIs was the strongest predictor of limbal temporal redness, followed by PAs (respectively, $P < 0.001$; $P = 0.019$). The use of beta-blockers was not associated with any of the redness score.

Discussion

Glaucoma is among the main causes of irreversible blindness worldwide and the majority of cases are treated medically, particularly in the early phase [15]. Therefore, numerous IOP-lowering eye drops have been developed overtime and are currently used by glaucoma patients, either in monotherapy or in combination. Although glaucoma medications are usually able to control IOP under the target value, certain therapies are characterized by unpleasant side effects, conjunctival hyperemia being the most frequent one.

In this study, we used Keratograph 5M to evaluate conjunctival redness in a large cohort of patients with glaucoma under topical IOP-lowering medications. Compared to control subjects, glaucoma patients showed a higher degree of conjunctival hyperemia measured either as global score and as sectorial score in nasal bulbar, temporal bulbar, nasal limbal and temporal limbal areas. Age, male sex and the number of active principles correlated with a higher degree of conjunctival hyperemia. In multiple regression analysis, the use of PAs, CAIs and AAAs was significantly associated with worse overall redness and nasal redness scores. Few previous studies evaluated the ocular surface status in patients under anti-glaucoma medications using the Keratograph 5M. A small observational study reported worse conjunctival hyperemia as well as TMH, break-up time and ocular discomfort symptoms in patients with glaucoma compared to control subjects [16]. A larger study including 211 patients with POAG concluded that age, number of daily eye drops and treatment with PAs contributed to the ocular redness [17]. In agreement with our results, the detrimental impact of medications upon redness was found to be higher on nasal sectors. This was interpreted as the consequence of the longer retention time of the drug in the nasal conjunctiva during its movement towards the lacrimal punctum [17].

The association between age and conjunctival hyperemia may be attributable to the gradual increase in tortuosity and to vessel wall remodeling occurring with ageing. However, we also observed higher redness scores in males compared to females among glaucoma patients. This finding is consistent

with few previous reports, but the causes are still not fully understood [18,19]. The difference in conjunctival hyperemia between genders may be at least partially due to sex hormones that have been shown to play a major role not only in the ocular surface homeostasis but also on endothelium-dependent and sympathetic control of microcirculation [20, 21].

In the multiple regression model, the use of CAIs was a stronger predictor of overall redness score compared to PAs. Similarly, AAAs and CAIs showed a stronger association with limbal redness scores than PAs. The lower influence of PAs on conjunctival hyperemia was an unexpected result, which disagrees with data from Pérez-Bartolomé and colleagues [17]. This inconsistency may be related to the use of different types of PAs in our cohort of patients. In fact, previous studies have demonstrated with subjective clinical scales that the type of PAs influence differently the amount of conjunctival hyperemia, and that latanoprost and tafluprost have lower effects compared to other agents such as bimatoprost 0.01% and travoprost [22, 23]. Our automated quantification of ocular redness confirmed a lower score in patients using latanoprost and tafluprost. However, this was a post hoc analysis and therefore it should be interpreted with caution.

Traditionally, preservatives such as benzalkonium chloride are thought to further contribute to the hyperemia induced by some active principles contained in the glaucoma medications. In fact, a lower incidence of conjunctival hyperemia has been subjectively detected in patients using preservative-free eye drops [24]. Moreover, switching from preservative-containing to preservative-free PAs was associated with a decrease of conjunctival hyperemia [25]. In our study, we did not detect any association between the use of preservatives and the redness scores. A similar finding was also reported by Pérez-Bartolomé and co-authors who employed the same automated instrument [17]. Thus, the effect of preservatives on conjunctival hyperemia may be less strong than previously thought. However, the limited number of patients using preservative free eye drops in this study could have hampered the detection of a statistically significant association and further data are desirable to better clarify this issue.

Although other automated systems have been developed, Keratograph 5M is currently the only commercially available device to measure conjunctival hyperemia objectively. The instrument may be useful in the clinical management of patients with glaucoma. In fact, ocular redness reduces patient's adherence to glaucoma therapy, and represents the most common symptom responsible for stopping or switching medications [26]. Therefore, the objective monitoring over time of ocular redness in glaucoma patients may be helpful to avoid the development of intense conjunctival hyperaemia that is known to compromise patient's adherence to therapy. In case of early detection of increased ocular redness, a therapeutic strategy to control hyperemia may be set. For instance, one possible approach is represented by intensive treatment with eyelid hygiene, oral free-acid supplementation, in particular omega-3 and flaxseed oil, and oral tetracycline derivate that may help to reverse ocular redness. This was recently demonstrated by a recent longitudinal study that followed glaucoma patients before and after the initiation of this therapeutic strategy [27]. Another possible therapy consists of modifying ongoing therapy, switching from preserved to unpreserved drugs, or changing active principle(s) used.

Finally, it should be pointed out that Keratograph 5M is able to investigate different clinical parameters of the ocular surface at the same time, such as infrared meibography, non-invasive tear film break-up time, tear meniscus height and lipid layer thickness. Thus, the device provides a comprehensive non-invasive evaluation of the ocular surface that can be easily applied also in the setting of glaucoma patients under medical treatment.

This study suffers from some important limitations. Firstly, it is known that lifestyle habits of patients, such as rural/urban, outdoor/indoor activity or alcohol use, may also affect ocular hyperemia. Nevertheless, these data were not collected in the study, thus it was not possible to carry out further evaluation. Secondly, the small sample of patients treated with preservative-free drops did not allow a sub-analysis that would have been helpful to clarify the direct effect of the active principles on eye redness. Further studies with larger sample sizes are required to address this issue. In addition,

although we enrolled a large cohort of patients, different treatment regimens were used and the sample size was not large enough to include all the variables in the multiple regression analysis. For this reason, we were unable to compare the impacts of each single active principle on the redness scores. Additionally, we did not include in the multiple regression analysis systemic medications and concomitant systemic diseases that may have had an impact on ocular redness. Finally, the use of an automatic technique compared with subjective evaluation could result in a reduced inter- and intra-observer variation. However, the absence of subjective evaluation represents a further limitation of the study.

In conclusion, glaucoma patients under topical IOP-lowering medications showed higher global and sectorial scores of ocular redness compared to matched control subjects. The number of active principles and the use of PAs, CAIs and AAAs contributed to a higher degree of conjunctival hyperemia.

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d. Conflict of Interests: None

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Figure Legend

Figure 1 – Representative images of ocular redness from a control subject (Part A) and 2 glaucoma patients using different medications (Parts B and C). Part A: Control subject (female; 65 years old; no medications) with a global redness score of 0.6. Part B: Glaucoma patient (female; 63 years old; topical beta-blockers twice a day) with a global redness score of 1.1. Part C: Glaucoma patient (male; 76 years old; prostaglandin analogues once a day) with a global redness score of 2.4.