Risk Factors for Optic Disc Hemorrhage in the Low-Pressure Glaucoma Treatment Study

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- PURPOSE: To investigate risk factors for disc hemorrhage detection in the Low-Pressure Glaucoma Treatment Study.
- DESIGN: Cohort of a randomized, double-masked, multicenter clinical trial.
- METHODS: Low-Pressure Glaucoma Treatment Study patients with at least 16 months of follow-up were included. Exclusion criteria included untreated intraocular pressure (IOP) of more than 21 mm Hg, visual field mean deviation worse than ~16 dB, or contraindications to study medications. Patients were randomized to topical treatment with timolol 0.5% or brimonidine 0.2%. Stereophotographs were reviewed independently by 2 masked graders searching for disc hemorrhages. The main outcomes investigated were the detection of disc hemorrhage at any time during follow-up and their recurrence. Ocular and systemic risk factors for disc hemorrhage detection were analyzed using the Cox proportional hazards model and were tested further for independence in a multivariate model.
- RESULTS: Two hundred fifty-three eyes of 127 subjects (mean age, 64.7 ± 10.9 years; women, 58%; European ancestry, 71%) followed up for an average ± standard deviation of 40.6 ± 12 months were included. In the multivariate analysis, history of migraine (hazard ratio [HR], 5.737; P = .007), narrow neuroretinal rim width at baseline (HR, 2.91; P = .048), use of systemic β-blockers (HR, 5.585; P = .036), low mean systolic blood pressure (HR, 1.06; P = .02), and low mean arterial ocular perfusion pressure during follow-up (HR, 1.172; P = .007) were significant and independent risk factors for disc hemorrhage detection. Treatment randomization was not associated with either the occurrence or recurrence of disc hemorrhages.
- CONCLUSIONS: In this cohort of Low-Pressure Glaucoma Treatment Study patients, migraine, baseline narrower neuroretinal rim width, low systolic blood pressure and mean arterial ocular perfusion pressure, and use of systemic β-blockers were risk factors for disc hemorrhage detection. Randomization assignment did not influence the frequency of disc hemorrhage detection. (Am J Ophthalmol 2014;157:945–952. © 2014 by Elsevier Inc. All rights reserved.)

GLAUCOMA IS A DEGENERATIVE OPTIC NEUROPATHY characterized by progressive loss of retinal ganglion cells and their axons, resulting in characteristic optic disc changes and visual field (VF) loss.1,2 Although elevated intraocular pressure (IOP) is the most important known risk factor for onset and progression,3–7 glaucoma develops in a sizable subset of patients despite untreated IOPs in the statistically defined normal range.8–11 Low-pressure glaucoma is a term used to describe that segment of patients with primary open-angle glaucoma whose untreated IOPs are always 21 mm Hg or less by Goldmann applanation tonometry.8

The Low-Pressure Glaucoma Treatment Study12–15 was a multicenter, double-masked, prospective, randomized clinical trial that investigated VF outcomes in low-pressure glaucoma patients treated either with a topical β-adrenergic antagonist (timolol maleate 0.5%) or an α2-adrenergic agonist (brimonidine tartrate 0.2%). The subjects randomized to topical brimonidine 0.2% were less prone to have VF progression than those treated with timolol 0.5%, despite similar IOP levels during the follow-up period.14 However, the explanation for this outcome remains unclear, and a possible neuroprotective effect of brimonidine 0.2%, a detrimental effect of timolol 0.5%, or both were hypothesized.14,15

Disc hemorrhage is a feature of glaucomatous optic neuropathy commonly observed in low-pressure glaucoma and rarely found in normal eyes.16–21 The association between glaucoma and disc hemorrhage was reported first by Bjerrum in 1889,16 and after the seminal work by Drance and Begg in 1970,16 it became the subject of numerous publications.17–21,23–30 Characterized by splinter-like or flame-shaped hemorrhage at or adjacent to the optic nerve
head, disc hemorrhage is an important risk factor for the onset and progression of glaucomatous optic neuropathy, particularly in low-pressure glaucoma. Given that the pathogenesis of disc hemorrhage has not yet been elucidated completely, recognition of the risk factors associated with disc hemorrhage may contribute to our understanding of the mechanisms involved in its occurrence. Based on the Low-Pressure Glaucoma Treatment Study findings, we hypothesized that among these risk factors, medical treatment with timolol 0.5% may be associated with a higher rate of disc hemorrhage occurrence than brimonidine 0.2%.

In the present study, we investigated the baseline and intercurrent risk factors associated with disc hemorrhage onset and recurrence among participants enrolled in the Low-Pressure Glaucoma Treatment Study. In addition, we investigated whether randomization to timolol maleate 0.5% or brimonidine tartrate 0.2% influenced the rate of disc hemorrhage occurrence.

**METHODS**

THE METHODOLOGY OF THE LOW-PRESSURE GLAUCOMA Treatment Study, including baseline characteristics and study design, have been described in detail elsewhere. In brief, the study was a multicenter, prospective clinical trial in which patients were randomized to treatment with topical brimonidine tartrate 0.2% versus timolol maleate 0.5%. The institutional review boards at all 13 participating centers approved the study protocol, and informed consent was obtained from all participants enrolled in the Low-Pressure Glaucoma Treatment Study. The study was registered in the clinical trials registry of the United States National Institutes of Health (http://www.clinicaltrials.gov; no. NCT00317577).

**INCLUSION AND EXCLUSION CRITERIA:** Study patients had a diagnosis of low-pressure glaucoma that fulfilled the following eligibility criteria: all known daytime untreated IOP of 21 mm Hg or less, open iridocorneal angles, at least 2 reproducible VFs with glaucomatous defects in 1 or both eyes on standard automated perimetry (Humphrey Field Analyzer; Carl Zeiss Meditec, Inc, Dublin, California, USA), with the location of the defect being consistent with the photographic appearance of the optic nerve head, and age of 30 years or older. To determine eligibility based on IOP, all patients receiving IOP-lowering treatment underwent a 4-week washout without therapy. Baseline IOP (measured with a calibrated Goldmann applanation tonometer) had to be 21 mm Hg or less in both eyes with less than a 3-mm Hg difference between the eyes on office diurnal curve (8:00 AM, 10:00 AM, noon, 4:00 PM) assessed before randomization.

Ocular exclusion criteria included the following: a history of IOP of more than 21 mm Hg in the patient record, best-corrected visual acuity worse than 20/40 in either eye, a history of angle closure or an occludable angle by gonioscopy, prior glaucoma incisional surgery, inflammatory eye disease, prior ocular trauma, diabetic retinopathy or other diseases capable of causing VF loss or optic nerve deterioration, extensive glaucomatous VF damage with a mean deviation worse than −16 decibels (dB), or a clinically determined threat to central fixation in either eye. Systemic exclusion criteria included a resting pulse of fewer than 50 beats/minute, severe or uncontrolled cardiovascular, renal, or pulmonary disease that would preclude safe administration of a topical β-adrenergic antagonist (β-blocker), and a prior myocardial infarction or stroke. Since the number of visits (and hence number of optic disc stereophotographs) influences the rate of disc hemorrhage detection, and to minimize the confounding effect of higher dropout rates in the brimonidine group, only those eyes with at least 16 months of follow-up were included in the analyses.

**RANDOMIZATION, TREATMENT, AND MASKING:** Patients were assigned randomly to receive monotherapy with either brimonidine tartrate 0.2% (Alphagan; Allergan, Inc, Irvine, California, USA) or timolol maleate 0.5% (Timoptic; Merck & Co, Inc, West Point, Pennsylvania, USA) twice daily in both eyes, including the morning before each visit. To allow for higher patient attrition in the brimonidine group attributable to an expected rate of adverse events of approximately 20%, randomization and delivery of medications (provided by Allergan, Inc) to the sites were stratified in blocks of 7 (4 to brimonidine and to 3 timolol). The randomization list was maintained, and masked study medications were provided in new 10-mL white bottles labeled with the assigned randomization number directly to the clinical centers by an independent pharmacy (Fountain Valley Cancer Center Pharmacy, Fountain Valley, California, USA). Ocular treatment other than the study medication was not permitted. Investigators, patients, and the VF and optic disc reading centers were all masked to patient assignment.

End points requiring discontinuation from the study included: treated IOP of more than 21 mm Hg that was confirmed within 1 month, safety concern as judged by the treating physician, symptomatic ocular allergic adverse events (hyperemia, pruritus, stinging, conjunctival folliculosis, or a combination thereof) requiring medication cessation, retinal events that could alter visual acuity or VF (e.g., age-related macular degeneration), the occurrence of systemic (e.g., respiratory or cardiovascular) adverse events that prevented the administration of topical timolol, nonocular intolerable events associated with topical brimonidine (e.g., xerostomia, fatigue, drowsiness), or if the patient moved or declined to continue participation. Data collection from discontinued patients ceased at their final study visit. Data up to this point were included in the analysis, but discontinued patients were no longer followed up as part of the study.
STUDY VISITS: Patients were examined at 1 and 4 months after initiation of treatment. Subsequent visits were at 4-month (±2 weeks) intervals. Prerandomization and postrandomization morning visits recorded the following: ocular and systemic history, blood pressure, pulse, corrected visual acuity, IOP, slit-lamp examination results, and optic disc evaluation for cup-to-disc ratio, neuroretinal rim characteristics, and the presence of disc hemorrhage. Gonioscopy and stereoscopic optic disc photographs were performed annually. Full-threshold standard achromatic perimetry (Humphrey 24-2) VF was performed at 4-month intervals according to protocol guidelines.

OUTCOME MEASURES: A disc hemorrhage was defined as a splinter- or flame-shaped hemorrhage adjacent to the optic disc border, on or within the retinal nerve fiber layer or neuroretinal rim. If peripheral to the disc margin, it needed to be contiguous with the β-zone parapapillary atrophy when this feature was present. The main outcome measures were (1) the detection of disc hemorrhage at any time during follow-up (occurrence) and (2) the reappearance of disc hemorrhage during follow-up in eyes with a prior disc hemorrhage after resolution of the initial disc hemorrhage (recurrence). Stereophotographs were reviewed independently by 2 glaucoma specialists (D.S.G., J.M.L.) searching for disc hemorrhages, and in cases of disagreement, a consensus between examiners was required for adjudication.

We examined clinical characteristics that predicted the occurrence of disc hemorrhage. The following demographic and ocular parameters were investigated: age at baseline, sex, family history of glaucoma, central corneal thickness, cup-to-disc ratio (estimated during slit-lamp funduscop examination), refractive error spherical equivalent, and lens status. Prerandomization data collected and investigated for risk assessment were: IOP mean, peak, and fluctuation during the diurnal curve; baseline pulse frequency; baseline systolic and diastolic blood pressures; presence of systemic comorbidities (migraine, Raynaud phenomenon, systemic hypertension, and diabetes mellitus); and use of systemic medications (categorized as systemic antihypertensives, systemic β-blockers, and antidiabetic agents). Postrandomization variables consisted of series length (ie, follow-up time); detection of at least 1 disc hemorrhage on stereophotographs any time during follow-up; mean, peak, and fluctuation of IOP; and blood pressure during follow-up. For numerical variables, the mean was calculated by averaging all values recorded during the follow-up period. Fluctuation was defined as the standard deviation of all measurements in the same interval. Mean ocular arterial perfusion pressure was estimated by the equation:

\[
\text{Mean arterial ocular perfusion pressure} = \frac{2}{3} \times (\text{diastolic blood pressure} + \frac{1}{3} \times (\text{systolic blood pressure} \quad - \quad \text{diastolic blood pressure}) \quad - \quad \text{IOP})
\]

Data on systemic comorbidities and medications were obtained from participants’ self-report.

STATISTICAL ANALYSIS: Descriptive statistics are presented with frequency tables and graphs, whereas estimates of center and dispersion are described as mean and standard deviation, respectively. If eligible, both eyes of the same patient were included in the analyses. A Cox proportional hazards model was used to test the relationship between predictors and the outcome (disc hemorrhage in either eye: yes or no), accounting for differences in follow-up duration. First, a univariate model independently testing each predictor was constructed using the aforementioned clinical variables. Variables with \( P < .25 \) in the univariate analysis were entered in the multivariate analysis, along with other predictors previously reported as being associated significantly with disc hemorrhage detection. Because mean arterial ocular perfusion pressure, systolic blood pressure, and diastolic blood pressure are correlated variables, they should not be entered together in the same multivariate model (ie, colinearity). Therefore, 2 different multivariate models were performed using a backward elimination approach based on the Wald test: one model that included the blood pressure parameters (model 1) and the other including mean arterial ocular perfusion pressure (model 2). Computerized statistical analyses were performed using SPSS for Windows version 16.1 (IBM SPSS Statistics, Inc, Armonk, New York, USA), and the \( \alpha \) level was set at 0.05 (2-sided).

RESULTS

OF 193 PATIENTS ASSESSED FOR ELIGIBILITY IN THE LOW-PRESSURE GLAUCOMA Treatment Study, 178 were randomized to treatment with either timolol or brimonidine. The characteristics of the study population have been described in detail elsewhere. Of those, 253 eyes of 127 subjects (mean age, 64.7 ± 10.9 years; women, 58%; European ancestry, 71%) met the inclusion and exclusion criteria for this study (at least 16 months of follow-up) and were followed up, on average, for 40.6 ± 12 months. Therefore, the following results refer to this subset of participants (127 patients; 253 eyes), whose clinical characteristics have been published previously. A total of 18 (7.1%) of 253 eyes of 15 (11.8%) of 127 patients experienced at least 1 disc hemorrhage during follow-up. Three patients (20%) had disc hemorrhages in both eyes (2 in the timolol group and 1 in the brimonidine group). Five eyes (27.8%) had a single disc hemorrhage event, 4 eyes (22.2%) had 2 disc hemorrhages, 2 eyes (11.1%) had 3 disc hemorrhages, and 7 eyes (38.9%) had 4 or more disc hemorrhages. With regard
to the number of eyes experiencing disc hemorrhage, 12 (8.6%) of 138 eyes in the timolol group had at least 1 disc hemorrhage, compared with 6 (5.2%) of 115 eyes in the brimonidine group (P = .33, Fisher exact test). Recurrent disc hemorrhage occurred in 10 (83.3%) of 12 timolol eyes and in 3 (50%) of 6 brimonidine eyes (P = .26). With regard to the number of patients experiencing disc hemorrhage, 10 (14.4%) of 69 patients in the timolol group had at least 1 disc hemorrhage, compared with 5 (8.6%) of 58 patients in the brimonidine group (P = .41). Recurrent disc hemorrhage occurred in 9 (90%) of 10 timolol patients and in 2 (40%) of 5 brimonidine patients (P = .07).

Univariate analysis showed that a history of migraine (hazard ratio [HR], 4.371; P = .01), low systolic blood pressure (HR, 1.041; P = .043), and low mean arterial ocular perfusion pressure (HR, 1.129; P = .015) were significant risk factors for the occurrence of disc hemorrhage. In addition, we observed that treatment randomization to either timolol or brimonidine did not influence these outcomes significantly (for timolol: HR, 1.64; P = .33). These results are summarized in Table 1.

### Table 1. Univariate Analysis of Ocular and Systemic Risk Factors for Occurrence of Disc Hemorrhage in Treated Low-Pressure Glaucoma Patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization to brimonidine 0.2%</td>
<td>0.607</td>
<td>0.228 - 1.618</td>
<td>.319</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.005</td>
<td>0.962 - 1.048</td>
<td>.825</td>
</tr>
<tr>
<td>Systemic arterial hypertension</td>
<td>1.115</td>
<td>0.440 - 2.825</td>
<td>.819</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.998</td>
<td>0.229 - 4.348</td>
<td>.997</td>
</tr>
<tr>
<td>History of migraine</td>
<td>4.371</td>
<td>1.431 - 13.333</td>
<td>.01</td>
</tr>
<tr>
<td>History of Raynaud phenomenon</td>
<td>1.902</td>
<td>0.551 - 6.579</td>
<td>.309</td>
</tr>
<tr>
<td>Use of systemic β-blockers</td>
<td>1.351</td>
<td>0.391 - 4.673</td>
<td>.634</td>
</tr>
<tr>
<td>Spherical equivalent (per diopter)</td>
<td>1.051</td>
<td>0.889 - 1.244</td>
<td>.56</td>
</tr>
<tr>
<td>Central corneal thickness (per μm)</td>
<td></td>
<td>0.988 - 1.014</td>
<td>.897</td>
</tr>
<tr>
<td>Vertical cup-to-disc ratio (per 0.1 unit)</td>
<td>0.212</td>
<td>0.01 - 4.464</td>
<td>.319</td>
</tr>
<tr>
<td>Narrower neuroretinal rim width at baseline</td>
<td>2.046</td>
<td>0.794 - 5.291</td>
<td>.138</td>
</tr>
<tr>
<td>Mean follow-up intraocular pressure (per mm Hg)</td>
<td>0.906</td>
<td>0.728 - 1.127</td>
<td>.374</td>
</tr>
<tr>
<td>Mean follow-up systolic blood pressure (per mm Hg)</td>
<td>1.041</td>
<td>1.001 - 1.081</td>
<td>.043</td>
</tr>
<tr>
<td>Mean follow-up diastolic blood pressure (per mm Hg)</td>
<td>1.058</td>
<td>0.980 - 1.14</td>
<td>.145</td>
</tr>
<tr>
<td>Mean follow-up heart rate (per beats/minute)</td>
<td>0.99</td>
<td>0.936 - 1.047</td>
<td>.729</td>
</tr>
<tr>
<td>Mean follow-up ocular perfusion pressure (per mm Hg)</td>
<td>1.129</td>
<td>1.024 - 1.244</td>
<td>.015</td>
</tr>
</tbody>
</table>

Statistically significant P Values are in bold.

### Table 2. Multivariate Analysis of Ocular and Systemic Risk Factors in the Model 1 for Occurrence of Disc Hemorrhage in Treated Low-Pressure Glaucoma Patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization to brimonidine 0.2%</td>
<td>0.298</td>
<td>0.08 - 1.115</td>
<td>.072</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>1.48</td>
<td>0.415 - 5.263</td>
<td>.546</td>
</tr>
<tr>
<td>History of migraine</td>
<td>5.737</td>
<td>1.46 - 22.727</td>
<td>.012</td>
</tr>
<tr>
<td>History of Raynaud phenomenon</td>
<td>3.476</td>
<td>0.837 - 14.493</td>
<td>.086</td>
</tr>
<tr>
<td>Use of systemic β-blockers</td>
<td>5.585</td>
<td>1.119 - 27.778</td>
<td>.036</td>
</tr>
<tr>
<td>Narrower neuroretinal rim width at baseline</td>
<td>2.91</td>
<td>1.008 - 8.403</td>
<td>.048</td>
</tr>
<tr>
<td>Mean intraocular pressure (per mm Hg)</td>
<td>0.84</td>
<td>0.654 - 1.079</td>
<td>.172</td>
</tr>
<tr>
<td>Mean systolic blood pressure (per mm Hg)</td>
<td>1.06</td>
<td>1.009 - 1.1122</td>
<td>.02</td>
</tr>
<tr>
<td>Mean diastolic blood pressure (per mm Hg)</td>
<td>1.054</td>
<td>0.967 - 1.151</td>
<td>.228</td>
</tr>
<tr>
<td>Mean follow-up heart rate (per beats/minute)</td>
<td>0.962</td>
<td>0.887 - 1.042</td>
<td>.34</td>
</tr>
</tbody>
</table>

Statistically significant P Values are in bold.
In the multivariate analysis, our first model (model 1) demonstrated that a history of migraine (HR, 5.737; \( P = .042 \)) or in model 2 (for timolol: HR, 2.53; \( P = .021 \)), narrower neuroretinal rim width at baseline (HR, 2.881; \( P = .042 \)), and low mean arterial ocular perfusion pressure during follow-up (HR, 1.172; \( P = .007 \)) were relevant and independent risk factors for the occurrence of disc hemorrhage (Table 2). In model 2, we observed that a history of migraine (HR, 4.716; \( P = .021 \)), narrower neuroretinal rim width at baseline (HR, 2.881; \( P = .042 \)), and low mean arterial ocular perfusion pressure during follow-up (HR, 1.172; \( P = .007 \)) were relevant and independent risk factors for episodes of disc hemorrhage in low-pressure glaucoma (Table 3). Consistent with the univariate analysis, treatment randomization did not affect the occurrence of disc hemorrhage in model 1 (for timolol: HR, 3.59; \( P = .056 \)) or in model 2 (for timolol: HR, 2.53; \( P = .082 \); see Tables 2 and 3).

**TABLE 3. Multivariate Analysis of Ocular and Systemic Risk Factors in the Model 2 for Occurrence of Disc Hemorrhage in Treated Low-Pressure Glaucoma Patients**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard Ratio</th>
<th>Minimum</th>
<th>Maximum</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization to brimonidine 0.2%</td>
<td>0.411</td>
<td>0.135</td>
<td>1.247</td>
<td>.116</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>1.948</td>
<td>0.615</td>
<td>6.173</td>
<td>.257</td>
</tr>
<tr>
<td>History of migraine</td>
<td>4.716</td>
<td>1.283</td>
<td>17.544</td>
<td>.021</td>
</tr>
<tr>
<td>History of Raynaud phenomenon</td>
<td>2.641</td>
<td>0.683</td>
<td>10.526</td>
<td>.169</td>
</tr>
<tr>
<td>Use of systemic ( \beta )-blocker</td>
<td>4.302</td>
<td>0.943</td>
<td>19.608</td>
<td>.06</td>
</tr>
<tr>
<td>Narrower neuroretinal rim width at baseline</td>
<td>2.881</td>
<td>1.038</td>
<td>8</td>
<td>.042</td>
</tr>
<tr>
<td>Mean follow-up ocular perfusion pressure (per mm Hg)</td>
<td>1.172</td>
<td>1.044</td>
<td>1.316</td>
<td>.007</td>
</tr>
</tbody>
</table>

Statistically significant \( P \) Values are in bold.

**DISCUSSION**

ALTHOUGH DISC HEMORRHAGE OCCURRENCE IS NOT A PATHOGENOMIC SIGN OF PROGRESSION IN GLAUCOMA—BECAUSE NOT ALL EYES WITH DISC HEMORRHAGE PROGRESS—THE STRONG ASSOCIATION BETWEEN THEM SHOULD BE CONSIDERED WHEN DISCUSSING RISK FACTORS FOR ONE OR THE OTHER, BECAUSE THEY OFTEN OVERLAP. IN ADDITION, IT REMAINS UNCLEAR WHETHER RISK FACTORS DESCRIBED FOR VF PROGRESSION \(^{11,15}\) ARE THE SAME AS THOSE THAT CONTRIBUTE TO GLAUCOMATOUS STRUCTURAL CHANGES OVER TIME. THIS STUDY AIMS TO IDENTIFY OCULAR AND SYSTEMIC RISK FACTORS FOR THE OCCURRENCE OF DISC HEMORRHAGE IN THE LOW-PRESSURE GLAUCOMA TREATMENT STUDY POPULATION. WE FOUND THAT A HISTORY OF MIGRAINE, LOW SYSTOLIC BLOOD PRESSURE, LOW MEAN ARTERIAL OCULAR PERFUSION PRESSURE, USE OF SYSTEMIC \( \beta \)-BLOCKERS, AND NARROWER NEURORETINAL RIM WIDTH AT BASELINE CONSTITUTED INDEPENDENT RISK FACTORS. AMONG THESE PREDICTORS, A HISTORY OF MIGRAINE, LOW SYSTOLIC BLOOD PRESSURE, AND USE OF SYSTEMIC \( \beta \)-BLOCKERS ARE IOP-INDEPENDENT PARAMETERS, WHICH SUPPORTS THE CONTRIBUTION OF MECHANISMS OTHER THAN OR IN ADDITION TO IOP IN THE PATHOGENESIS OF DISC HEMORRHAGE IN LOW-PRESSURE GLAUCOMA.\(^{8,16,19,36}\)

OUR FINDINGS ARE, AT LEAST IN PART, CONSISTENT WITH PREVIOUS STUDIES.\(^{15,36}\) IN A STUDY OF 432 PRIMARY OPEN-ANGLE GLAUCOMA EYES, JONAS AND ASSOCIATES DEMONSTRATED THAT A SMALLER OPTIC DISC NEURORETINAL RIM AREA WAS A MORPHOLOGIC PARAMETER ASSOCIATED WITH THE OCCURRENCE OF DISC HEMORRHAGE AND SUGGESTED THAT DISC HEMORRHAGES ARE SEEN MORE OFTEN IN EYES WITH THINNER RIMS.\(^{35}\) IN OUR STUDY, NEURORETINAL RIM DAMAGE AT BASELINE ALSO WAS AN INDEPENDENT RISK FACTOR FOR DISC HEMORRHAGE IN LOW-PRESSURE GLAUCOMA, AND ITS PRESENCE INCREASED THE RISK OF DISC HEMORRHAGE DETECTION BY APPROXIMATELY 3-FOLD IN BOTH MULTIVARIATE MODELS. IN ANOTHER STUDY, KIM AND ASSOCIATES SHOWED THAT SYSTEMIC BLOOD PRESSURE PLAYS A ROLE IN THE ONSET OF DISC HEMORRHAGE.\(^{30}\) HOWEVER, UNLIKE OUR FINDINGS, THEY FOUND THAT THE ONLY SIGNIFICANT RISK FACTOR FOR DISC HEMORRHAGE OCCURRENCE IN LOW-PRESSURE GLAUCOMA WAS SYSTEMIC HYPERTENSION. THIS APPARENT DISCREPANCY BETWEEN STUDIES COULD BE EXPLAINED BY (1) DIFFERENCES REGARDING STUDY DESIGN, BECAUSE THOSE INVESTIGATORS APPLIED A RETROSPECTIVE ANALYSIS; (2) FACTORS RELATED TO GENETICS—EUROPEAN ANCESTRY WAS PREDOMINANT IN OUR STUDY COMPARED WITH ASIAN ANCESTRY IN THEIRS; AND (3) THE FACT THAT BEING DIAGNOSED (AND TREATED) WITH SYSTEMIC HYPERTENSION DOES NOT PRECLUDE PATIENTS FROM ACTUALLY HAVING LOW BLOOD PRESSURE DURING FOLLOW-UP, PARTICULARLY NIGHTTIME DIPS. IT IS NOTEWORTHY THAT IN THEIR STUDY, BLOOD PRESSURE READINGS WERE NOT COLLECTED DURING FOLLOW-UP AS WE DID. Thus, they might have overlooked the blood pressure-lowering effect of the antihypertensive medications in those patients. Overtreatment of systemic hypertension may lead to a series of complications including stroke and reduction of ocular perfusion pressure.\(^{39,41}\) Moreover, treatment for systemic hypertension has been reported as a risk factor for incident glaucoma\(^{35}\) and VF progression in established disease.\(^{5,15}\)

THE EARLY MANIFEST GLAUCOMA TRIAL, WHICH INCLUDED PATIENTS WITH NEWLY DIAGNOSED GLAUCOMA RANGING FROM LOW TO HIGH IOP, FOUND THAT FEMALE GENDER, MYOPIA, AND...
lower baseline or follow-up IOP were independent risk factors for disc hemorrhage detection. The Early Manifest Glaucoma Trial investigators did not investigate these risk factors further in the subgroup of eyes with low-pressure glaucoma. In our study, these variables did not reach statistical significance.

The association between low-pressure glaucoma and a history of migraine headache has been suggested in previous publications. Corbett and associates found that 44% of their low-pressure glaucoma sample reported a history of migraine. In a questionnaire-based study that investigated migraine in low-pressure glaucoma, high-pressure primary open-angle glaucoma, ocular hypertensive, and normal subjects, the low-pressure glaucoma group had a greater prevalence of migraine than the other groups. Moreover, in the Collaborative Normal Tension Glaucoma Study, migraine was a risk factor for functional progression in patients with low-pressure glaucoma. In the present study, we demonstrated that migraine is a predictor for the occurrence of disc hemorrhage. Migraine is associated with transient cerebral vasospastic episodes that can result in impairment in the mechanisms of autoregulation of blood flow in the central nervous system. Neuroimaging studies suggest that silent cerebral infarct, which is an infarct in the brain incidentally detected in individuals without clinical neurologic signs, can be found in patients with migraine and low-pressure glaucoma. In addition, low-pressure glaucoma patients with silent cerebral infarct had faster rates of VF deterioration than those without, suggesting the role of ischemic injury in glaucoma progression. Autoregulation may be inefficient in patients with glaucomatous optic neuropathy and may result in varying degrees of ischemia at the optic nerve. This could predispose one to microinfarction at the optic nerve head and the occurrence of disc hemorrhage. Therefore, those studies support our results, because migraine seems to be a clinical marker of an impaired microvascular autoregulation. One limitation of the present study is that the diagnosis of migraine was based on self-report during standardized interview. Therefore, the number of patients with this condition in our sample is unknown, which could have influenced its statistical significance.

In one of our models, use of systemic β-blockers was a predictor of disc hemorrhage detection. Systemic β-blockers are known to be less effective than other antihypertensive medications in decreasing the rates of ischemic events, such as myocardial infarction and stroke. Thus, one could hypothesize that β-blockers would not offer enough protection to the optic nerve head tissues regarding ischemia-related events and may predispose patients to the occurrence of disc hemorrhage. Further, overtreatment for systemic hypertension increases the risk of coronary ischemia and mortality, and likewise could be deleterious to the optic nerve head by decreasing the mean arterial ocular perfusion pressure. An alternative explanation is that systemic β-blocker use contributed to a reduced IOP-lowering efficacy in eyes receiving topical timolol 0.5%, predisposing them to disc hemorrhage. Nevertheless, it is important to stress that our study did not aim to investigate the specific role of systemic antihypertensives on disc hemorrhage occurrence, because information regarding the dosage, posology, duration of treatment, and 24-hour blood-pressure monitoring was not collected as part of the Low-Pressure Glaucoma Treatment Study protocol. Future studies are warranted to assess these variables, how they affect the 24-hour blood-pressure pattern, and the risk of progression in low-pressure glaucoma.

Although low-pressure glaucoma patients treated with timolol 0.5% progressed faster than those treated with brimonidine 0.2%, we found no difference in the frequency of disc hemorrhage detection in the present analysis. Although not statistically significant, there were more disc hemorrhage events in eyes receiving timolol compared with eyes receiving brimonidine. Our study may have been underpowered to detect differences regarding the frequency of disc hemorrhage, and this should be taken into consideration when interpreting our results. The Low-Pressure Glaucoma Treatment Study sample size calculation was aimed to test differences in rates of progression, and not disc hemorrhage occurrence, and hence the present ancillary analysis may not have had sufficient statistical power for disc hemorrhage detection. It is also possible that we would have detected a difference in disc hemorrhage occurrence between the 2 treatments in a longer study. The mean follow-up in the Low-Pressure Glaucoma Treatment Study was only 40.6 ± 12 months, because of higher-than-expected dropout resulting from adverse reactions to the medication. A study with larger sample size, longer follow-up time, and more frequent optic disc photography would be necessary to prove or refute the role of the type of medication on disc hemorrhage occurrence and recurrence.

In summary, we demonstrated that a history of migraine, narrower neuroretinal rim width at baseline, low systolic blood pressure or low mean arterial ocular perfusion pressure, and use of systemic β-blockers are risk factors for the occurrence of disc hemorrhage in treated low-pressure glaucoma patients. The finding that variables unrelated to IOP were associated with the occurrence of disc hemorrhage underscores the role of IOP-independent factors in the pathogenesis of disc hemorrhage in low-pressure glaucoma.
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MEMBERS OF THE LOW-PRESSURE GLAUCOMA STUDY GROUP

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