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

RAFAEL L. FURLANETTO, CARLOS GUSTAVO DE MORAES, CHRISTOPHER C. TENG, JEFFREY M. LIEBMANN, DAVID S. GREENFIELD, STUART K. GARDINER, ROBERT RITCH, AND THEODORE KRUPIN, FOR THE LOW-PRESSURE GLAUCOMA TREATMENT STUDY GROUP

• 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; $P = .012$), narrower 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.)

Accepted for publication Feb 2, 2014.

From the Einhorn Clinical Research Center, New York Eye and Ear Infirmary, New York, New York (R.L.F., C.G.D.M., C.C.T., J.M.L., R.R.); the Department of Ophthalmology, New York University School of Medicine, New York, New York (C.G.D.M., C.C.T., J.M.L.); the Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Palm Beach Gardens, Florida (D.S.G.); the Devers Eye Institute, Legacy Health, Portland, Oregon (S.K.G.); the Department of Ophthalmology, New York Medical College, Valhalla, New York (R.R.); the Department of Ophthalmology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois (T.K.); and The Chicago Center for Vision Research, Chicago, Illinois (T.K.).

Inquiries to Carlos Gustavo De Moraes, Department of Ophthalmology, New York University School of Medicine, 310 East 14th Street, New York, NY 10003; e-mail: demoraesmd@gmail.com

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 IOP within 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 Study[12–15] 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 α_2-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,[22] 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

0002-9394/$36.00
http://dx.doi.org/10.1016/j.ajo.2014.02.009

head, disc hemorrhage is an important risk factor for the onset[25] and progression[26–29] of glaucomatous optic neuropathy, particularly in low-pressure glaucoma.[30,31] 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,[14,15] 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.[12] 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 5-mm Hg difference between the eyes on an 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,[16,17] 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%,[32,33] 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.