The Relationship between Intraocular Pressure Reduction and Rates of Progressive Visual Field Loss in Eyes with Optic Disc Hemorrhage

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Purpose: To evaluate rates of visual field progression in eyes with optic disc hemorrhages and the effect of intraocular pressure (IOP) reduction on these rates.

Design: Observational cohort study.

Participants: The study included 510 eyes of 348 patients with glaucoma who were recruited from the Diagnostic Innovations in Glaucoma Study (DIGS) and followed for an average of 8.2 years.

Methods: Eyes were followed annually with clinical examination, standard automated perimetry visual fields, and optic disc stereophotographs. The presence of optic disc hemorrhages was determined on the basis of masked evaluation of optic disc stereophotographs. Evaluation of rates of visual field change during follow-up was performed using the visual field index (VFI).

Main Outcome Measures: The evaluation of the effect of optic disc hemorrhages on rates of visual field progression was performed using random coefficient models. Estimates of rates of change for individual eyes were obtained by best linear unbiased prediction (BLUP).

Results: During follow-up, 97 (19%) of the eyes had at least 1 episode of disc hemorrhage. The overall rate of VFI change in eyes with hemorrhages was significantly faster than in eyes without hemorrhages (−0.88%/year vs. −0.38%/year, respectively, $P<0.001$). The difference in rates of visual field loss pre- and post-hemorrhage was significantly related to the reduction of IOP in the post-hemorrhage period compared with the pre-hemorrhage period ($r = -0.61$; $P<0.001$). Each 1 mmHg of IOP reduction was associated with a difference of 0.31%/year in the rate of VFI change.

Conclusions: There was a beneficial effect of treatment in slowing rates of progressive visual field loss in eyes with optic disc hemorrhage. Further research should elucidate the reasons why some patients with hemorrhages respond well to IOP reduction and others seem to continue to progress despite a significant reduction in IOP levels.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.
Ophthalmology 2010;117:2061–2066 © 2010 by the American Academy of Ophthalmology.

Optic disc hemorrhages have long been associated with glaucomatous damage, and recent evidence from prospective randomized clinical trials has confirmed their role as risk factors for development and progression of the disease.[1–11] In the Ocular Hypertension Treatment Study, the risk of developing glaucoma in eyes with ocular hypertension and disc hemorrhages was 6 times higher than in those without a disc hemorrhage.[10] In the Collaborative Normal Tension Glaucoma Study and the Early Manifest Glaucoma Trial (EMGT), glaucomatous eyes with disc hemorrhages experienced significantly more visual field progression during follow-up than eyes without hemorrhages.[6,11]

Although the role of disc hemorrhages as a risk factor for glaucoma progression seems well-established, the benefit of reducing intraocular pressure (IOP) in halting progression in eyes with optic disc hemorrhages has not been completely elucidated. Studies by Miyake et al[12] and Hendrickx et al[13] suggested that IOP reduction by surgical or medical therapy significantly decreased the frequency of optic disc hemorrhages in patients with open-angle glaucoma. However, a recent report from the EMGT did not find a significant relationship between IOP-lowering treatment and presence of disc hemorrhages, even though IOP-lowering treatment was efficacious in delaying or avoiding progressive visual field loss.[11] Both the treatment and control groups experienced similar frequencies and incidence of optic disc hemorrhages during follow-up. The EMGT investigators reported no significant interaction between treatment group and disc hemorrhages with regard to time to progression, which would suggest that despite not reducing the frequency of hemorrhages, treatment would still have a similar protective effect in patients with and without disc hemorrhages.

The EMGT used an event-based method for analysis of visual field progression with an all-or-nothing measure of change: the glaucoma change probability maps.[14] It is possible that a quantitative analysis of rates of change would reveal differences in progression in eyes with optic disc hemorrhages depending on the level of IOP reduction. Eval-

ISSN 0161-6420/10/$–see front matter
doi:10.1016/j.ophtha.2010.02.015

uation of rates of change in these patients would potentially allow a more accurate assessment of the risk of development of significant functional impairment in relation to life expectancy.

The current study evaluates the rates of visual field progression in eyes with optic disc hemorrhages and the effect of IOP reduction on these rates.

Materials and Methods

This was an observational cohort study. Participants from this study were included in a prospective longitudinal study designed to evaluate optic nerve structure and visual function in glaucoma (Diagnostic Innovations in Glaucoma Study [DIGS]) conducted at the Hamilton Glaucoma Center, University of California, San Diego. Participants in the DIGS were longitudinally evaluated according to a preestablished protocol that included regular follow-up visits in which patients underwent clinical examination and several other imaging and functional tests. All the data were entered in a computer database. All participants from the DIGS study who met the inclusion criteria described below were enrolled in the current study. Informed consent was obtained from all participants. The University of California San Diego Human Subjects Committee approved all protocols, and the methods described adhered to the tenets of the Declaration of Helsinki.

Subjects were followed annually. At each visit during follow-up, subjects underwent a comprehensive ophthalmologic examination, including review of medical history, best-corrected visual acuity, slit-lamp biomicroscopy, IOP measurement, gonioscopy, dilated fundoscopic examination, stereoscopic optic disc photography, and automated perimetry using Full-Threshold or Swedish Interactive Threshold Algorithm. Only subjects with open angles on gonioscopy were included. Subjects were excluded if they presented best-corrected visual acuity less than 20/40, spherical refraction outside $\pm$ 5.0 diopters or cylinder correction outside 3.0 diopters, or any other ocular or systemic disease that could affect the optic nerve or visual field.

The study included eyes that were diagnosed with glaucoma at the baseline visit and that had a minimum follow-up time of 3 years. Eyes were classified as glaucomatous if they had repeatable (at least 2 consecutive) abnormal visual field test results, defined as a pattern standard deviation outside of the 95% normal confidence limits or a Glaucoma Hemifield Test result outside normal limits, regardless of the appearance of the optic disc. Visual fields were evaluated by masked glaucoma experts to exclude potential artifacts, such as learning effects, eyelid, or lens rim artifacts. Eyes were also classified as glaucomatous if they had evidence of glaucomatous optic neuropathy based on masked assessment of optic disc stereophotographs. Signs of glaucomatous damage to the optic nerve were considered diffuse or localized neuroretinal rim loss, excavation, and retinal nerve fiber layer defects.

The presence of optic disc hemorrhage was evaluated by masked assessment of optic disc stereophotographs. Two experienced graders evaluated simultaneous stereoscopic optic disc photographs (TRC-SS; Topcon Instrument Corp of America, Paramus, NJ), and each grader was masked to the subject's identity and the other test results. All included photographs were judged to be of adequate quality or better. Discrepancies between the 2 graders were resolved by consensus or adjudication by a third experienced grader. Disc hemorrhages had to be located within 1 disc diameter from the optic disc border and not associated with optic disc edema, papillitis, diabetic retinopathy, central or branch retinal vein occlusion, or any other retinal disease.

Evaluation of rates of visual field change during follow-up was performed using the visual field index (VFI).[15] Details of the calculation of the VFI have been described.[15] In brief, the VFI represents the percent of normal age-corrected visual function and is intended for use in calculating rates of progression and staging glaucomatous functional damage. Evaluation of rates of functional loss in glaucoma eyes with the VFI has been demonstrated to be less susceptible than the mean deviation to the effects of cataract or diffuse media opacities.[15] Also, the VFI is supposed to more accurately reflect the relative importance of the central and more peripheral visual fields to patient visual function compared with other available global visual function indexes. The VFI can range from 100% (normal visual field) to 0% (perimetrically blind field).

Statistical Analysis

The evaluation of the effect of optic disc hemorrhages on rates of visual field progression was performed using random coefficients models. These models are a type of linear mixed model that involves both random intercepts and slopes and that takes into account the clustered structure of the data allowing the residuals associated with the longitudinal measures on the same unit of analysis to be correlated. The details on the use of these models for evaluation of rates of change in glaucoma and to model longitudinal processes have been reported.[16–20]

Estimates of rates of change for individual eyes were obtained by best linear unbiased prediction (BLUP), which have many advantages over ordinary least square estimates. Ordinary least square estimates can be imprecise in eyes with just a few measurements available over time or with large intraindividual variability.[18] Individual ordinary least square estimates (i.e., individual regression lines) also do not take into account the information provided by the whole population, whereas BLUPs are shrinkage estimates that take into account the results obtained by evaluating the whole sample of eyes, giving less weight to estimates obtained from eyes with few measurement occasions or large intraindividual variability (i.e., more "noise").[21] In eyes with a large number of measurements over time, BLUP and ordinary least square estimates give similar results. We have previously used BLUPs to estimate individual rates of structural change measured by different instruments in glaucoma.[16] Others have reported the use of BLUPs to estimate rates of cognitive change in longitudinal models for diseases such as Alzheimer's disease.[22]

Statistical analyses were performed using STATA v. 11.0 (StataCorp, College Station, TX). The alpha level (type I error) was set at 0.05.

Results

The study included 510 eyes of 348 patients with glaucoma who were followed for an average of 8.2 years (median: 7.6 years, first quartile: 5.0 years, third quartile: 10.9 years). During follow-up, 97 (19%) of the eyes had at least 1 episode of disc hemorrhage. Table 1 shows demographic and clinical variables in eyes that had at least 1 episode of disc hemorrhage compared with eyes that did not have disc hemorrhages during follow-up. Eyes that developed optic disc hemorrhages had worse disease severity at baseline, as indicated by mean deviation, pattern standard deviation, VFI, and vertical cup/disc ratio values. Figure 1 shows the number of optic disc hemorrhages observed over time.

We initially analyzed the effect of disc hemorrhages on rates of visual field progression considering the whole duration of follow-up for each eye. Eyes were divided on the basis of the presence (yes/no) of disc hemorrhages at any time during follow-up. Eyes with optic disc hemorrhages and eyes without hemorrhages had significant rates of visual function loss over time. However, the overall rate of VFI change in eyes with hemorrhages was significantly faster than in eyes without hemorrhages (-0.88%/year vs. -0.38%/year, respectively, $P<0.001$). There