Disc Hemorrhages and Treatment in the Early Manifest Glaucoma Trial.

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Title: Disc Hemorrhages and Treatment in the Early Manifest Glaucoma Trial

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Abstract

Purpose: To evaluate the effect of intraocular pressure (IOP)-reducing treatment on the development of disc hemorrhages in glaucoma patients.
Design: Prospective cohort study of Early Manifest Glaucoma Trial patients, followed up to 11 years (median=8 years).
Participants: Newly detected glaucoma patients randomized to argon laser trabeculoplasty plus betaxolol (n=129) or no initial treatment (n=126), followed every three months with tonometry, perimetry and ophthalmoscopy, and with fundus photography every 6 months.
Methods: Logistic regression expressed as odds ratios (OR) and 95% confidence intervals (CI), analysis of variance, and Cox time-dependent models, expressed as Hazard Ratios (HR) and CI.
Main outcome measures: Presence (yes/no) and frequency of disc hemorrhages.
Results: Disc hemorrhages were identified in approximately 55% of all patients, whether by ophthalmoscopy or reviewing photographs. In analyses including data up to the time of progression, disc hemorrhages were equally common among treated and control patients: 51.2% vs. 45.2% respectively (p=0.34) based on ophthalmoscopy, and 50.4% vs. 44.4% (p=0.34) based on photographs. Gender was the only factor related to presence of disc hemorrhages detected both by ophthalmoscopy, OR=0.48 (CI=0.26–0.88) (p= 0.022), and on photographs, OR=0.64 (CI=0.38–1.09) (p= 0.099) for male patients. Frequency of disc hemorrhages over time did not differ between treated and control patients: 8.4% vs. 8.5% respectively (p=0.93) based on ophthalmoscopy, and 12.4% vs. 11.2% (p=0.36) based on photographs. Disc hemorrhages were significantly associated with time to progression, HR=1.02 (CI=1.01–1.04), and there was no evidence of interaction between treatment group and disc hemorrhages.
Conclusion: IOP-reducing treatment was unrelated to the presence or frequency of disc hemorrhages. Our results may suggest that disc hemorrhages cannot be considered an indication of insufficient IOP-lowering treatment, and that glaucoma progression in eyes with disc hemorrhages cannot be totally halted by IOP reduction. Results also suggest that disc hemorrhages do not occur in all glaucoma patients.

Introduction

The association between splinter-shaped hemorrhages on the optic disc rim and glaucoma is well-known.[1] However, it is unclear whether disc hemorrhages appear in all glaucoma patients,[2,3] or just in a subpopulation.[1,4,5] In almost all reports, disc hemorrhages are considered a sign of active glaucoma,[2,6,7] which then would increase the likelihood of progression.[7-,15]

A number of studies have reported increased frequencies of disc hemorrhages at lower levels of intraocular pressure (IOP).[3,5,12,16-19] Higher IOP, on the other hand, increases the risk for progression.[15,20] In the Early Manifest Glaucoma Trial (EMGT), patients with lower IOP had slower progression than patients with elevated IOP, and IOP-lowering treatment delayed progression in all patients, regardless of IOP level; [21] furthermore, the presence of disc hemorrhages at follow-up was a significant factor for progression.[14,15] It is, therefore, interesting to investigate whether IOP reduction, the current treatment for glaucoma, has any effect on the development of disc hemorrhages in glaucoma patients included in EMGT. To our knowledge, only two papers have reported on the effect of IOP-reducing treatment on the incidence of disc hemorrhages in glaucoma pateints.[22,23]The limited literature on this issue is probably explained by the fact that almost all glaucoma patients are treated for long periods of time, and very few randomized studies have followed untreated glaucoma patients.[21, 24] Thus, the need to intensify IOP-lowering treatment to prevent progression in eyes with disc hemorrhages, as commonly suggested,[7,11,25, 26] is based on rather weak evidence.

The main purpose of this report is to study the effect of IOP-reducing treatment on the presence and frequency of disc hemorrhages in glaucoma patients randomized to treatment or no treatment. Data originate from EMGT, a clinical trial with the primary aim of evaluating the effectiveness of IOP reduction in newly detected, previously untreated glaucoma. The patients were randomized to IOP-reducing treatment or no treatment and prospectively followed. The presence of observed disc hemorrhages was recorded every 3 months in clinical forms and fundus photographs were obtained every 6 months for up to 11 years. The EMGT database is therefore unique and suitable for evaluating the relationship of treatment to the occurrence of disc hemorrhages.

Patients and Methods

Overview

The EMGT included 255 newly detected glaucoma patients, who were randomized to argon laser trabeculoplasty plus betaxolol (n=129) or no initial treatment (n=126). After randomization, patients were followed every three months for up to 11 years (median= 8 years). The study visit included IOP measurement with the Goldmann applanation tonometer, perimetry with the Humphrey Field Analyzer 30-2 Full Threshold program (Carl Zeiss Meditec, Inc., Dublin, CA), best corrected visual acuity, and a comprehensive eye examination including ophthalmoscopy. The observers had to assess details from the upper and lower disc halves separately and to complete pre-printed forms asking specifically for disc hemorrhages among other possible disc features. Fundus photographs were obtained every 6 months.

The study was conducted according to the tenets of the declaration of Helsinki. All patients gave informed consent, and the Ethics Committee of Lund University, Sweden, and the Committee on Research Involving Human Subjects at the State University of New York at Stony Brook approved the study.

All disc hemorrhages observed by ophthalmoscopy at the regular visits were recorded in the clinical study forms. After closure of EMGT two trained graders, masked for patient identity and any study variable, independently reviewed all photographs in random order. The observers evaluated a total of 7,554 photographs for disc hemorrhages. There was good agreement between the two observers, kappa = 0.70 (0.67 - 0.72). A lack of agreement between the graders was settled by a third expert observer through adjudication.

Glaucoma progression was defined by predetermined criteria for visual fields; that is, at least 3 identical test point locations showing significant deterioration in 3 consecutive tests.[27] During the first 9 years of the study, glaucoma progression could also be defined by deterioration of the optic disc, as assessed by two masked independent graders at a Disc Photography Reading Centre.

Outcome measures and statistical analyses
This report is based on study data obtained up to March 31, 2004. In the current report, one eye per patient was included in the analyses. In patients with one eligible eye, only that eye was considered, in patients where both eyes were eligible, the first progressing eye was considered, or if neither eye progressed (or both progressed at the same time) the worse eye of the baseline measurements (IOP and mean deviation) was considered. This approach is identical to that applied in previous EMGT reports.[14,15]

For the current report, one major outcome was the ever presence of disc hemorrhages, which was measured by determining whether patients ever had a disc hemorrhage (yes/no), whether at baseline or follow-up. Another major outcome was the frequency of disc hemorrhages, which was measured by the number and percent of disc hemorrhages at follow-up visits. The analyses followed several steps.

First, the agreement between disc hemorrhage data obtained by ophthalmoscopy and from disc photographs was compared using McNemar's test. For these comparisons, clinical forms without photographic counterparts were not considered.

-Second, the ever presence of disc hemorrhages in treated and control patients was initially compared using Chi-Square statistics to test the association between treatment status and ever presence of disc hemorrhages. In all analyses including comparisons between treatment and control groups, all patients were censored for progression, i.e., no data were included from control patients after progression, a time when their treatment could be initiated.

-Third, analyses were conducted to evaluate potential factors related to the presence of disc hemorrhages ever recorded in clinical forms and, separately, on photographs. These factors were: treated or control group, age, gender, baseline IOP, mean follow-up IOP, IOP change (baseline IOP minus IOP at last visit), baseline perimetric mean deviation (MD), central corneal thickness, exfoliation status, baseline refractive error, one or two eyes eligible, baseline systolic

blood pressure, baseline diastolic blood pressure, history of hypertension, hypertension medication, cardiovascular disease history, low blood pressure history, Raynaud's disease history, migraine history, current smoking, prior smoking, glaucoma family history, baseline systolic perfusion pressure, baseline diastolic perfusion pressure , and mean baseline perfusion pressure. Associations were tested using multivariable logistic regression and expressed by odds ratios (OR) and 95% confidence intervals (CI). The analysis was performed using stepwise selection; the final model included factors with $p<0.10$. The format of variables representing the factors was continuous whenever possible.

Fourth, the same set of factors, plus interactions, was tested for association with frequency of disc hemorrhages from baseline to time for progression or last visit, calculated as percent of visits with disc hemorrhages in clinical forms or in photographs using analysis of variance (ANOVA). Linear regression with a stepwise model selection procedure similar to above was used.

Finally, associations with time to glaucoma progression were evaluated including the same factors as those included in the analyses for association with disc hemorrhages (cf. above) with Cox regression models. In these analyses, the percent of disc hemorrhages at study visits was calculated and used as a time-dependent covariate.

Results

Patients were followed for up to 11 years. The median number of visits was 28. Ninety-six percent of the 255 patients had 10 or more visits, and in 92% of all patients 10 or more photographs from the study eye were available.

Comparison of clinical and photographic assessments
The number of patients with ever observed disc hemorrhages was similar by ophthalmoscopy (141/255) and by review of photographs (140/255) ($p=0.862$), approximately 55% with both methods (55.3% by ophthalmoscopy and 54.9% by review of photographs). There was good agreement between disc hemorrhage recordings in clinical forms and on photographs, kappa = 0.74 (95% confidence intervals: 0.66-0.82). When considering the frequency of disc hemorrhages at any of the follow-up visits with both clinical and photographic data (n=3777), they were recorded in 9.2% of the clinical forms and detected on 12.5% of the photographs, a significant difference ($p<0.0001$).

Comparison between study groups
Based on either method of assessment, IOP-reducing treatment was not associated with presence (yes/no) of disc hemorrhages in EMGT patients; furthermore, the frequency of disc hemorrhages at study visits over time also did not differ between the treated and control groups (Table 1).

Table 1. Disc hemorrhages in the treated and control groups by ophthalmoscopic and photographic assessment

Presence of disc hemorrhages in individual patients (n=255)	Treated group (n=129) n (%)	Control group (n=126) n (%)	P-value

Clinical forms*			
Yes	66 (51.2)	57 (45.2)	0.356
No	63 (48.8)	69 (54.8)	
Photographs			
Yes	65 (50.4)	56 (44.4)	0.342
No	64(49.6)	70 (55.6)	
Frequency of disc hemorrhages at study visits (n=2390)			
Clinical forms*	111 (8.4)	91 (8.5)	0.943
Photographs	164 (12.4)	120(11.2)	0.356

*Clinical forms from visits without photographs were excluded

Factors related to the presence of disc hemorrhages

The factors associated with the ever presence of disc hemorrhages, as recorded in clinical forms, were: a) refractive error, with more disc hemorrhages in myopic eyes: OR=0.74 per diopter for hyperopic eyes (CI= 0.63-0.88), p=0.0005; b) lower baseline IOP: OR= 0.92 per mmHg (CI = 0.86-0.99), p= 0.03 (or lower follow-up IOP, OR= 0.89, (CI=0.82-0.97), p=0.01; and c) female gender: OR=0.48 for male patients (CI=0.26-0.90), p=0.022. A trend was also observed for higher baseline systolic blood pressure: OR =1.15 per mmHg (CI = 0.98 to 1.35), p=0.098. In the analysis based on photographs, the only suggested association with disc hemorrhages was for female gender: OR=0.64 (CI= 0.38–1.09), p=0.099.

To further evaluate associations between presence of disc hemorrhages and IOP reduction, we compared the extent of IOP decrease in treated patients with vs. without disc hemorrhages. Both groups had a similar extent of IOP reduction (approximately 4.5 mmHg), which was unrelated to disc hemorrhages noted in clinical forms or photographs (p=0.23 and p=0.37, respectively). In addition, the linear regression analyses were repeated, based on treated patients only and not censoring for progression. These analyses involved the same variables, but included IOP change (baseline IOP minus IOP at the last visit). The results showed no association between presence of disc hemorrhages and extent of IOP change, OR= 1.00 (CI=0.90-1.11), p= 1.00 for clinical data and OR=0.99 (CI: 0.89-1.10) p= 0.88 for photographic data.

Factors related to the frequency of disc hemorrhages

In patients with at least one observed disc hemorrhage, 70% had two or more recorded in clinical forms, and 63% on photographs (Fig. 1). After censoring for progression, 67% had two or more disc hemorrhages noted in forms and 57% on photographs. The factors associated with higher percent frequency of disc hemorrhages recorded in clinical forms were: lower baseline IOP (p=0.015) (or lower mean follow-up IOP, p= 0.038), and current smoking (p=0.006). The same results were found based on photographic data (lower baseline IOP; p=0.023 (or lower mean follow-up IOP, p= 0.104), and current smoking; p=0.000).

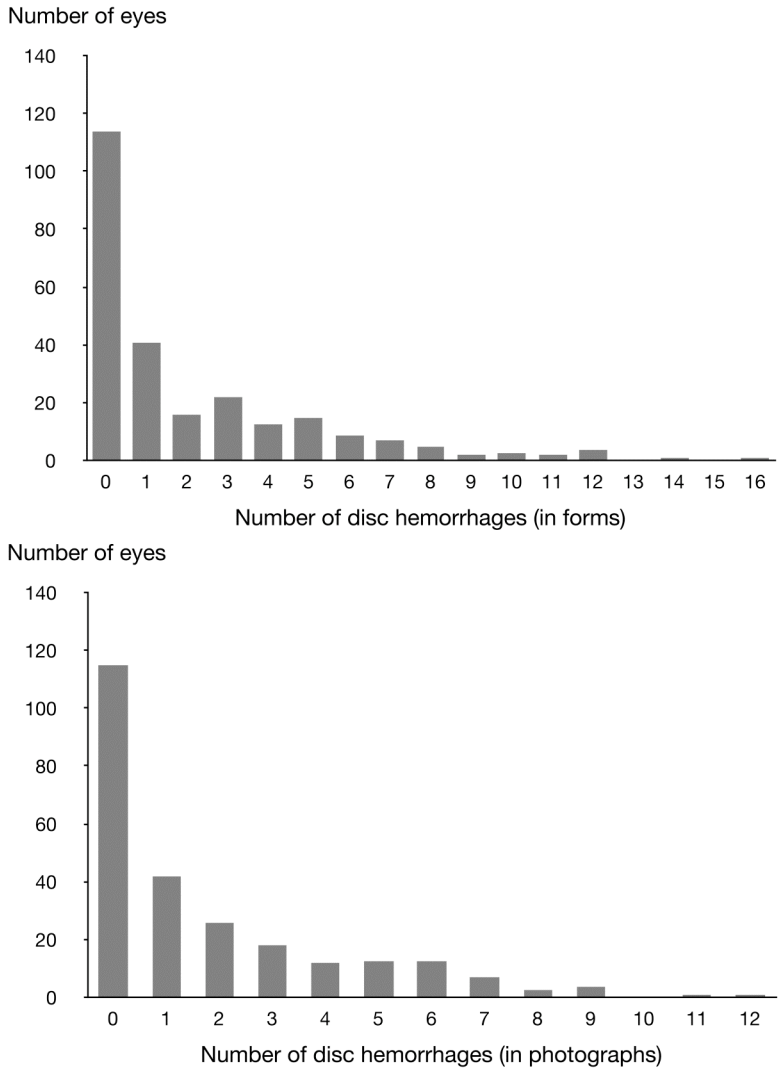

Fig. 1. About 45% of all patients had no observed disc hemorrhages in clinical forms (n=114) or photographs (n=115). Most patients with disc hemorrhages had relatively few disc hemorrhages during follow-up, considering the large number of visits: 76% had ≤5 hemorrhages recorded in clinical forms (top) and 79% had ≤5 in photographs (bottom).

These linear regression analyses were also repeated among treated patients to determine possible relationships between frequency of disc hemorrhages and IOP reduction. The models included the same variables, but used IOP change instead of baseline IOP or follow-up IOP. No significant associations were found (p=0.477 for clinical data; p=0.447 for photographic data). Additional analyses that included both baseline IOP and IOP change (or follow-up IOP and IOP change) continued to suggest that IOP change was not significantly related to disc hemorrhages.

Disc hemorrhages and progression

Patients with disc hemorrhages had significantly shorter time to progression, whether based on clinical or photographic data. Results based on clinical data were: HR=1.03 (CI=1.01-1.04), p=0.0001. Other factors also associated with significantly shorter time to progression in this same

model were older age, HR=1.38 (CI=1.02-1.88), p=0.039; exfoliation syndrome, HR=3.10 (CI=1.92-5.01), p<0.0001, and both eyes eligible, HR=1.94 (CI=1.39-2.71), p<0.0001. Prolonged time to progression in this same model was also suggested for: IOP-lowering treatment, HR=0.63 (CI=0.43-0.92), p=0.018. There was no interaction between treatment group and disc hemorrhages with regard to time to progression, HR=0.99 (CI= 0.97-1.02), p=0.53. In the model based on photographs, the same factors were statistically significant, except for older age, p=0.073.

Discussion

The presence and frequency of disc hemorrhages were not associated with IOP-reducing treatment, not even when including other factors in the model, e.g., IOP at baseline or follow-up, and interactions between IOP and treatment. Similarly, we found no relationship between disc hemorrhages and the extent of IOP decrease in treated patients. Our findings suggest that disc hemorrhages are related to the level of IOP at follow up, with low levels increasing risk, rather than to the amount of IOP reduction.

Our results are partially in conflict with those reported previously by Hendrickx et al., 1994,[22] which suggested that IOP-lowering agents reduced frequencies of disc hemorrhages in patients with high pressures, but not in normal tension glaucoma patients, and by Miyake et al., 2006,[23] who reported reduced frequency of disc hemorrhages after IOP-lowering surgery in both normal tension glaucoma patients and in high-pressure primary open angle glaucoma patents. Hendrickx and coworkers evaluated effects of anti-glaucoma medications in patients with normal tension glaucoma and suspect glaucoma, while Miyake et al. evaluated IOP-lowering effects of trabeculectomy in already treated glaucoma patients in a retrospective study including relatively few patients with disc hemorrhages (16 NTG and 18 POAG). The Ocular Hypertension Treatment Study reported slightly more observations of disc hemorrhages in their untreated group of ocular hypertensive patients (p=0.13).[28] The authors speculated whether the relatively small number of observed disc hemorrhages explained this non-significant result. In contrast, our findings are not explained by low numbers of disc hemorrhages, as approximately 55% of our patients had disc hemorrhages, and two or more disc hemorrhages were observed in 60 –70% of these patients.

In the present study, analyses of association between presence of disc hemorrhages and other factors, as assessed in photographs and in clinical forms, were not in total agreement. More factors were associated with presence of disc hemorrhages in clinical forms than in photographs; only gender was suggested as a factor in both analyses. We cannot explain this apparent discrepancy, but significant odds ratios were often rather close to 1, e.g., for IOP and blood pressure, while the odds ratio for gender was 0.48 in clinical forms and 0.64 in photographs. In contrast, no discrepancies between clinical and photographic-based results were observed when evaluating risk factors for frequency of disc hemorrhages, with both analyses indicating associations with lower baseline IOP (or mean follow-up IOP) and current smoking.

Furthermore, lower IOP was a factor associated with both presence and frequency of disc hemorrhages in most analyses, and this is in agreement with a number of previously published studies.[3,11,12,16, 18,19]

We identified almost the same number of patients having disc hemorrhages by reviewing photographs as by ophthalmoscopy, 140 vs. 141, that is about 55% of our patients. Somewhat more hemorrhages, not patients, were identified on photographs than by ophthalmoscopy, 12.5% vs. 9.2% respectively. Our result differs very much from that reported from the Ocular Hypertension Treatment Study,[28] where 84% of all patients with disc hemorrhages were identified only in photographs, and 16% by both clinical examinations and photographs. These differences may be due to our forms prompting ophthalmologists to answer separately whether disc hemorrhages were present or not, or to the fact that EMGT patients had manifest glaucoma and, therefore disc hemorrhages were much more likely than in the Ocular Hypertension Treatment Study.

In the current report we confirm our previous results that disc hemorrhages are associated with glaucoma progression,[14,15] and that IOP-reducing treatment increases time to progression.[21] Occurrence of disc hemorrhages is sometimes interpreted as a marker for insufficient IOP-lowering treatment, and more intense treatment is suggested in eyes with hemorrhages to prevent progression.[7,11,25,26] The results of our study, including patients randomized to treatment or no treatment and followed frequently for a long period (up to 11 years) do not support that interpretation. Results from the Collaborative Normal Tension Glaucoma Study in fact suggest that patients will benefit less from IOP-lowering treatment.[24] Neither presence of disc hemorrhages or their percent frequency at follow-up showed any association with IOP-lowering treatment, or with the extent of IOP reduction in treated patients. Since control patients progressed earlier, the potential effect of our censoring for progression would be a reduced chance to detect disc hemorrhages in control than treated patients. However, when considering all study visits, both groups of patients had very similar percent frequencies of disc hemorrhages

It is not clear whether disc hemorrhages occur in all glaucoma patients, or just in a subpopulation.[1,4,5] The chance to detect a disc hemorrhage increases with increasing number of observations. Krakau[3] constructed a statistical model for calculation of probability of detecting at least one disc hemorrhage after a certain number of examinations, and suggested that almost 90% of all patients ever having a disc hemorrhage should be detected after 10 examinations. The vast majority of our patients (>90%) had more than 10 observations. Despite this fact we were able to detect disc hemorrhages in about only 55% of all patients, which may suggest that disc hemorrhages do not occur in all glaucoma patients.

In conclusion, we were unable to demonstrate any effect of IOP-reducing treatment on presence or frequency of disc hemorrhages, despite a clear association between disc hemorrhages and glaucoma progression. This result may suggest that disc hemorrhages cannot necessarily be taken as a sign that a patient is receiving inappropriate IOP-lowering treatment and that glaucoma progression cannot be totally halted by IOP reduction in eyes with disc hemorrhages.

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