Lack of Visual Field Improvement After Initiation of Intraocular Pressure Reducing Treatment in the Early Manifest Glaucoma Trial

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Purpose. We evaluate how visual fields are affected by the initiation of IOP-reducing therapy in previously untreated glaucoma individuals.

Methods. Qualifying individuals with newly diagnosed glaucoma having normal to moderately elevated IOP were prospectively randomized either to IOP-reducing therapy or to no treatment. Before randomization, individuals underwent repeatedly Standard Automated Perimetry (SAP) testing and Goldmann tonometry. Three months after randomization, patients again underwent SAP and tonometry. Changes between baseline and the 3-month follow-up visit in the perimetric summary index, mean deviation (MD), and total deviation values at significantly depressed test points were compared between the treated and untreated groups.

Results. Of 255 individuals studied, 129 were randomized to treatment and 126 to no treatment. Intraocular pressure decreased by an average of 24% among treated and by 0.6% in the untreated patients. Mean deviation deteriorated slightly in both groups; mean change was −0.15 and −0.44 dB in the treated and untreated groups, respectively; the difference was not statistically significant, ($P = 0.16$). No association was seen between IOP reduction and change in MD. Sensitivities decreased slightly in significantly depressed test points, mean change was −0.45 dB in the untreated and −0.38 dB in the treated groups ($P = 0.88$).

Conclusions. Observed visual field changes among glaucoma patients receiving initial IOP-reducing therapy were not significantly different to changes seen in patients who received no treatment. Thus, our results did not support the idea that visual field status improves after initiation of IOP- reducing therapy in glaucoma individuals, at least not in individuals with initially normal to moderately elevated IOPs.

Keywords: glaucoma, visual field, intraocular pressure, therapy

If the visual fields of glaucoma individuals are followed long enough, they are likely to show some amount of deterioration. Intraocular pressure–lowering treatment has a positive effect, slowing, or at best preventing further deterioration. It has been suggested that glaucomatous visual field status can improve after initiation of IOP-reducing medical treatment or after surgery,[1–6] but the suggestion is equivocal. Improvement of glaucomatous visual field defects often can be explained by learning effects in individuals new to perimetry,[7,8] and continued perimetric learning over multiple years has been described even in perimetrically-experienced individuals.[9]

Several studies have reported both improvement and deterioration of visual fields after IOP- reducing interventions,[10–13] a result that might be explained by random test–retest variability commonly seen in eyes with glaucomatous field loss.[14]

One approach to settling the question might be to look for a positive correlation between IOP reduction and visual field improvement. Several studies have reported such correlations,[2,15–18] while other studies could not confirm these findings.[10–12,19–21] Comparisons between surgically treated glaucomatous eyes and control eyes have been reported in only a few studies.[17,22]

In the Early Manifest Glaucoma Trial (EMGT),[23] previously untreated individuals with newly diagnosed manifest glaucoma were randomized to IOP-reducing pharmacologic treatment plus laser trabeculoplasty, or to no treatment, and then regularly monitored with IOP measurements and perimetry. Since an untreated control group was followed prospectively with the same protocol as the treated group, the EMGT provides an unusual opportunity to study possible improvement of the visual field after initialization of IOP-reducing medical and laser treatment in individuals with manifest glaucoma.

Thus, the purpose of the current report was to assess possible improvement in visual fields after initialization of IOP-reducing treatment in newly diagnosed and previously untreated glaucoma.

Methods

Study Protocol

The EMGT (National Institutes of Health ClinicalTrials.gov identifier NTC00000132; Date of registration, September 23,

1999) was a randomized clinical trial of individuals with newly detected, previously untreated manifest open angle glaucoma. Individuals were eligible if they had newly diagnosed primary open angle glaucoma or exfoliative glaucoma with or without elevated IOP. The study design has been described in detail previously.[23] Briefly, individuals were randomized between 1993 and 1997 into one of two arms; treatment according to a fixed protocol with 0.5% betaxolol (Betoptic; Alcon Fort Worth, TX, USA) twice a day plus 360° argon laser trabeculoplasty, or to no treatment. After randomization, individuals were followed regularly with IOP measurements using the Goldmann applanation tonometer, and with Standard Automated Perimetry (SAP) using the 30-2 Full Threshold program of the Humphrey Field Analyzer (Carl Zeiss Meditec, Inc., Dublin, CA, USA). Examiners were masked to individual treatment status.

The EMGT was conducted according to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Lund University, Sweden, as well as by the Committee on Research Involving Human Subjects at the State University of New York at Stony Brook (Stony Brook, NY, USA). All individuals gave informed consent.

We identified 85% of included individuals through a large population-based screening of individuals between 50 to 80 years of age. The screening protocol included disc photography and Goldmann tonometry. The remaining 15% were referred from other ophthalmologists with the aim of investigating eligibility for inclusion in the EMGT. Inclusion in the EMGT required documentation of repeatable visual field defects compatible with a diagnosis of glaucoma in at least one eye. The definition of glaucomatous visual field loss was based on the Glaucoma Hemifield Test implemented in the Humphrey Field Analyzer. Individuals with advanced field loss, defined as a mean deviation (MD) value worse than −16 dB, were not eligible for inclusion. Most individuals had early field loss; the median baseline MD was −4.04 dB, and the interquartile range (IQR) was 4.0 dB. The eligibility rules specified that any condition precluding reliable visual fields or disc photography were reasons for noneligibility,[23] but no numbers were defined for unreliable fields, which must be considered an intelligent choice at that time, when, for example, individuals with high false-negative (FN) rates in glaucomatous fields were considered unreliable despite the fact that such rates mirror the state of the eye rather than the reliability of the individuals. Very few individuals were considered noneligible for EMGT based on unreliable fields; we do not have a number, but it should not be more than 1% or 2% of screened and otherwise eligible individuals. Eyes with lens opacities exceeding standard photographs nuclear (N) 1, cortical (C) 2, or posterior subcapsular (P) 1 in the Lens Opacities Classification System II (LOCS II)[24] were ineligible.

Individuals with a mean pretreatment IOP above 30 mm Hg, or a single measurement above 35 mm Hg, were not included in the EMGT. Mean untreated baseline IOP before randomization was 21 mm Hg, and ranged from 13 to 30 mm Hg.

Before baseline randomization, inclusion and exclusion criteria were checked at two separate postscreening visits, to determine eligibility. Both visits included visual field testing and IOP measurement of both eyes in all individuals. Thus, all individuals had undergone computerized visual field testing at least at two visits before the baseline visits. Baseline data were collected at two different visits; both visits included tonometry and perimetry. Baseline IOP and baseline visual field data were calculated as the means of the measurements obtained at the two visits. Individuals were randomized at the second baseline visit.

Analysis

The current report compares baseline perimetry and tonometry data with findings at the 3-month follow-up visit. Changes in visual fields were calculated as the difference in MD values between the 3-month visit and baseline. Differences in numeric change in MD values between the untreated and treated groups were compared. The numbers of eyes who improved in MD by ≥1, ≥2, or ≥3 dB were counted.

It may be logical to assume that IOP reduction could not improve test point locations with normal sensitivities. Therefore, changes in visual fields also were calculated as the difference in age-corrected threshold values at test points showing a significant depression at the $P < 1\%$ level (flagged as $P < 1\%$ or $P < 0.5\%$ in the total deviation probability maps) at any of the two baseline tests or at the 3-month follow-up test. The numerical change in dB was compared between the untreated and treated groups, and a subanalysis was performed of better or worse eyes as determined by median split of baseline MD.

Intraocular pressure reduction was calculated as the difference between the IOP value at the 3-month visit and the baseline IOP. The association between IOP reduction and change in MD was calculated by linear regression, separately for treated and untreated individuals. The association between age at baseline, untreated baseline IOP, and baseline MD on one hand and change in MD on the other hand was analyzed by linear regression analysis separately for the treated and the untreated groups.

In the 76% (194/255) of individuals who were enrolled on the basis of having manifest glaucoma in just one eye, findings in that eye were included in the analysis. In individuals with manifest glaucoma in both eyes, findings in both eyes were included in the analysis. Comparisons between treated and untreated groups were performed by the mixed models procedure with individuals as a random factor to adjust for possible dependence between the two eyes of the same individual. A P value <5% was considered to be statistically significant.

The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 22.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 255 individuals, 90 men and 165 women, was included in EMGT. Mean age at enrollment was 68 years, ranging from 50 to 79. Of the individuals, 129 were randomized to IOP-reducing treatment and 126 to no treatment. Three-month follow-up data were missing for two individuals, one randomized to treatment and the other to no treatment; thus, the results here are based on 312 eyes, 152 untreated and 160 treated, of 253 individuals.

Deterioration in MD was seen somewhat more often than improvement. The same proportion of eyes, 61% of treated and untreated eyes, had a worse MD at the 3-month visit than at baseline. The numerical changes in MD were small and negative, indicating a slight deterioration; the mean change was −0.15 dB (standard deviation [SD] = 1.52) among treated and −0.44 dB (SD = 2.05) among untreated eyes. The distributions of those changes were not statistically different ($P = 0.16$), and the proportions of patients improving by ≥1, ≥2, and ≥3 dB after 3 months also were the same or almost the same among untreated and treated eyes (see Table).

The median number of test points per eye with significantly depressed age-corrected threshold values at the $P < 1\%$ level was 10 (IQR = 13.25) at the first baseline test, 8 (IQR = 11.25)

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Table. Proportions of Eyes With Improved MD Values After Baseline at ≥1, ≥2, and ≥3 dB Levels

MD Improvement, dB	IOP Lowering Treatment	After 3 Mo. Follow-Up
≥1	Yes	16%
≥1	No	17%
≥2	Yes	9%
≥2	No	9%
≥3	Yes	4%
≥3	No	4%

Almost the same numbers were seen among treated and untreated patients.

at the second baseline test, and 9 (IQR = 13.75) at the 3-month follow-up tests among the untreated eyes, the corresponding numbers among the treated eyes were 11 (IQR = 14.75), 10 (IQR = 15.75), and 11 (IQR = 14). The numeric changes in age-corrected threshold values at those points were small and negative, indicating slight deterioration; the mean individual change was –0.45 dB (SD = 3.96) among untreated and –0.38 dB (SD = 3.26) among treated eyes ($P = 0.88$). The subanalysis of eyes that were better and worse at baseline, as indicated by MD, revealed no significant differences between treated and untreated eyes. The median deterioration of –0.14 dB (IQR = 3.63) for treated and –0.26 dB (IQR = 5.40) for untreated among those with worse MD ($P = 0.20$), and –0.31 dB (IQR = 4.07), and –0.02 dB (IQR = 4.70), respectively, for the ones with better MD ($P = 0.24$).

Mean baseline IOP was 20.7 mm Hg, with an SD of 4.1. At the 3-month visit mean IOP reduction was 24% for treated eyes and 0.8% for untreated control eyes. Intraocular pressure was reduced in most treated eyes; 81% had an IOP reduction ≥10%, 56% had a reduction ≥20%, 29% had a reduction ≥30%, 16% a reduction of ≥40 %, and 4% had an IOP reduction of ≥50%. Among the untreated controls, IOP was reduced by ≥10% in 23%, ≥20% in 5%, and ≥30% in 1%. Despite a clear reduction of IOP among most treated individuals, no association between IOP reduction and change in MD values was seen, the coefficient of determination (r^2) was 0.003 and similar to that in the untreated group, 0.004 (see Fig.).

Patient age was not significantly associated with change in MD in the untreated group. The slope of change in MD over age was –0.01 dB/y ($P = 0.72$), and the coefficient of determination (r^2) was only 0.001. In the treated group the slope was –0.05 dB/y, which reached borderline significance ($P = 0.05$), but r^2 was only 0.02, indicating a very small influence of age on deterioration from baseline to the 3-month follow-up test.

The untreated mean baseline IOP, ranging from 13 to 30 mm Hg, was not significantly associated with change in MD, neither for untreated nor treated eyes; the slopes were –0.04 dB/mm Hg ($P = 0.27$) and –0.09 dB/y ($P = 0.76$), respectively.

The mean and median baseline MD for all included eyes was –4.67 dB (SD = 3.56) and –4.04 dB (IQR = 4), respectively, ranging from –14.7 to +2.4 dB. Baseline MD was not significantly associated with change in MD in the untreated group; the slope was 0.01 dB/dB baseline MD ($P = 0.86$). In the treated group the slope was –0.1 dB/dB baseline MD ($P = 0.003$) with an r^2 of 0.06. The result among treated patients suggests slightly more deterioration in eyes starting at a better MD level than among eyes starting with a worse MD level.

Discussion

We were unable to detect any positive short-term influence of IOP reduction on visual fields in patients included in the EMGT, despite the fact more than 50% of treated individuals had IOP reductions of 20% or more, and as many as 15% had reductions of 40% or more (see Fig.). Small improvements in MD and in significantly depressed test points were just as common as small deteriorations and similar among treated and untreated controls. The upper limit of the 95% confidence interval for change in MD, representing the largest plausible improvement, was 2.5 dB for the treated and 4.0 dB for the untreated individuals. Thus, improvement in sensitivity was somewhat bigger among the untreated patients, suggesting that changes in sensitivity were explained by random variability rather than of the initiation of treatment. In aggregate, the visual fields of treated and control eyes deteriorated slightly, but deterioration was somewhat smaller in the treated than in the untreated group. We previously reported that the mean rate of progression among the untreated eyes was 1.08 dB/y,[25] and of course we know that in the longer follow-up, visual field progression occurred more often among untreated than among treated patients.[26,27] The magnitude of the small MD differences seen between baseline and the 3-month visit in the

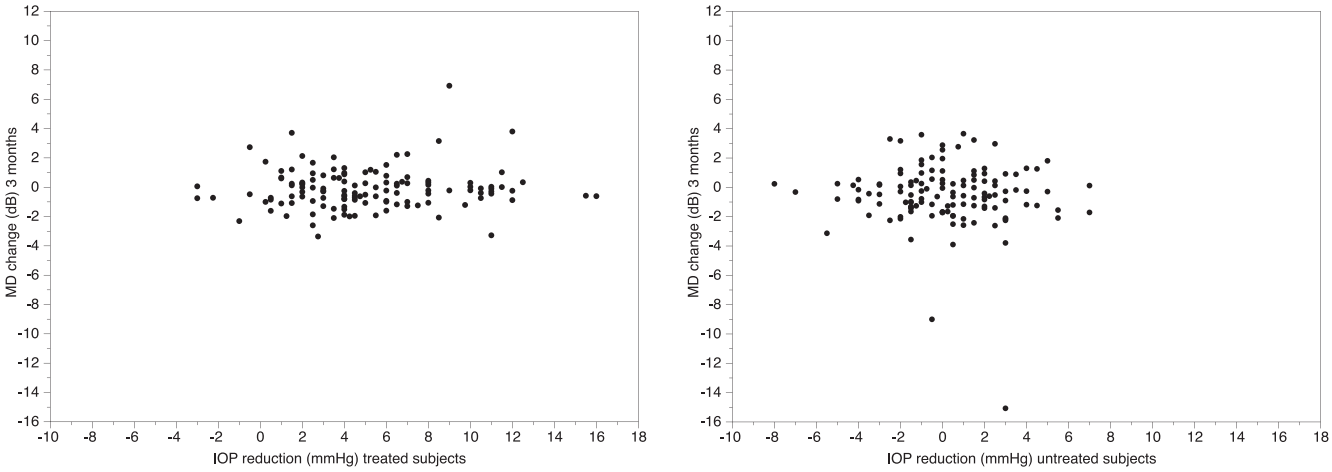

Figure. Changes in perimetric MD versus IOP reduction among treated individuals (*left*) and untreated controls (*right*). Almost all treated individuals had an IOP reduction, while approximately half of the untreated had no IOP reduction. There was no association between IOP reduction and change in MD; the slopes were almost flat; 0.02 dB/mm Hg reduction among the treated individuals ($P = 0.51$, $r^2 = 0.003$) and –0.05 dB/mm Hg reduction among untreated controls ($P = 0.46$, $r^2 = 0.004$).

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treated and the untreated groups is in agreement with what one could expect based on the long-term rate of progression and the risk reduction achieved with treatment.

As stated in the introduction the results from earlier studies on this topic are conflicting. We believe that our findings illustrated the importance of control groups when studying treatment effects on a disease like glaucoma, when the outcome variable is derived from a psychophysical test whose results are known to be affected by perimetric learning effect.[7,8]

In some clinical settings, treatment-associated MD improvements might be explained as regression to the mean, if eyes showing rapid deterioration and/or threatening elevations in IOP were to receive more or less immediate escalations in therapy, before confirmation of findings.

Lack of perimetric experience can be a confounder when assessing change in visual field series. In our study all EMGT patients had similar visual field testing experience before baseline testing. Sometimes, long-term or continued learning effects are seen,[7] but there is no reason to believe that continued learning effects would be different in patients randomized to treatment, compared to patients randomized to no treatment.

One study suggested that perimetric improvement after initiation of therapy occurs more often in younger individuals,[1] a finding we could not confirm. Among our patients there was no association between age and change in visual fields, but no patient younger than 50 years of age was included in the EMGT. It also has been reported that improvement occurs mostly in eyes with early visual field loss,[22] another finding that we were not able to confirm, but rather on the contrary finding a weak association between better baseline MD and more deterioration among the treated individuals, but the coefficient of determination, r^2, was only 0.06 indicating a vague association.

The present study has several strengths: It was a prospective study with an untreated control group. Tonometry was performed by personnel who did not know whether patients were treated or untreated. The treatment decision was not trigged by an observation of apparent deterioration; instead, all eyes were randomized regardless of IOP or field status.

The study also has one important weakness. No individuals included in the EMGT had any untreated IOP measurement values higher than 35 mm Hg, and baseline IOP values ranged from 13 to 30 mm Hg. Thus, we have no information on eyes with very high pretreatment IOPs, and we can only draw conclusions about eyes with normal to moderately increased pretreatment pressures. However, within that range, we could find no evidence of visual field improvement after IOP reduction.

In conclusion, we were unable to demonstrate any short-term association between therapeutic lowering of IOP and improvement in the visual field in treatment naive glaucoma patients in the EMGT cohort.

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