TheEffectofLong-TermIntraocularPressureReduction
onthedifferentialLightSensitivityinGlaucomaSuspects

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This study was undertaken to observe the effect on the differential light sensitivity in glaucoma suspects produced by a long-term reduction in intraocular pressure (IOP) with timolol maleate. The results are taken from an ongoing 6 year follow-up study of glaucoma suspects randomly selected for treatment and nontreatment. We present fine-grid meridional data, recorded every 4 months by automated perimetry, of all 46 patients (24 treated and 22 untreated) who completed the 6 year follow-up without developing localized visual field defects, acquired optic disc changes and whose IOP was not judged clinically dangerous during the follow-up. Methods of analyzing the profile sensitivity, the profile slope and the sensitivity of specific locations over the follow-up are described. The results show that the long-term fluctuation in differential light sensitivity in the two groups was not significantly different ($P = 0.395$) and that the sensitivity at most of the locations remained stable. The number of stable locations was not significantly different in the two groups ($P = 0.412$) and there was also no difference in the number of locations where the sensitivity appeared to decrease ($P = 0.193$) or increase ($P = 0.540$). Analysis of covariance showed no group difference in the profile sensitivity or the profile slope and that these variables remained stable in both groups over the 6 year period. Although the treated group maintained a consistently lower IOP than the untreated controls, our results showed that long-term pressure reduction with timolol in glaucoma suspects appeared not to influence the differential light sensitivity in the tested meridian.

Epidemiological studies have shown that the distribution of intraocular pressure (IOP) in the population is not Gaussian but is positively skewed.\textsuperscript{1-4} The positive tail, containing those with elevated IOP, is thought to consist of two groups, namely those individuals with manifest glaucoma who have associated optic disc and/or visual field changes and those who have normal discs and fields (often labelled ocular hypertensives) and referred to as glaucoma suspects in this paper.

To ascertain what proportion of glaucoma suspects proceed to frank glaucomatous damage, long-term follow-up studies of these individuals without pressure-reducing regimes have been reported.\textsuperscript{5-9} Most studies show that between 0\% and 10\% develop glaucoma; however, there are considerable variations in the population samples and length of follow-up. In a Swedish population sample,\textsuperscript{10} the annual incidence of manifest glaucoma in individuals with IOP below 20.5 mm Hg was 0.18\%, but in those with an IOP above 20.5 mm Hg the corresponding figure was 0.8\%.

The fact that patients with an elevated IOP are more likely to develop glaucomatous damage than those with a normal IOP, and yet 90\% or more of those with elevated IOP may never develop glaucomatous damage, poses a problem in the management of glaucoma suspects. The decision to lower the IOP in a glaucoma suspect depends on the level of IOP in addition to other risk factors. The probability of developing glaucomatous visual field defects in patients with pressures exceeding 30 mm Hg is significantly higher than in those with pressures between 21 and 25 mm Hg.\textsuperscript{7,11,12} Abnormality of the disc, the age of the patient and a positive family history of glaucoma are the other most commonly reported risk factors,\textsuperscript{6,13-15} but there are undoubtedly more.

Pressure reduction with epinephrine has been shown to reduce the risk of glaucomatous damage in suspect eyes with IOP exceeding 24 mm Hg.\textsuperscript{16} Larger scale studies\textsuperscript{7,17} have, however, shown that miotic therapy does not prevent visual field defects in glaucoma suspects. The treatment of all patients presenting solely with elevated IOP may be financially burdensome, inconvenient and more important, may expose them to potentially serious side effects.
The present study was conducted to determine if a long-term reduction in the IOP of glaucoma suspects with timolol maleate influences the differential light sensitivity. We present results of differential light sensitivities recorded at regular and frequent intervals of all glaucoma suspects, randomly assigned to treatment or nontreatment, who completed a 6 year follow-up without developing localized visual field defects or acquired optic disc changes. We describe a method of analyzing meridional perimetric data and apply these techniques to elucidate possible differences between the two groups of patients.

Materials and Methods

The patients were drawn from an ongoing study comparing the incidence of the development of glaucomatous visual field defects and optic disc changes in two groups of glaucoma suspects, one group whose IOPs were reduced with timolol and the other whose IOPs were not treated.

Patients with a visual acuity poorer than 20/50 (6/15) in either eye, or who had ocular or neurological disease capable of producing visual field defects were not admitted to the study. Patients with cardiac failure, chronic pulmonary disease, bradycardia (<50 beats per minute) and those receiving systemic beta blockers were likewise excluded.

The inclusion criteria were: (1) Untreated IOP ≥ 22 mm Hg on three separate days, usually within 2 weeks. (A small number of prospective patients on pressure-reducing medication for suspect glaucoma were given a “washout” period of 3-4 weeks). (2) No features of acquired optic disc change such as focal notching or disc hemorrhage, or a cup/disc ratio asymmetry ≥0.2 determined by stereophotography. (3) Normal visual fields using the modified Armaly technique8,11 on the Goldmann perimeter. In addition, normal visual fields on the Perimetron (Coherent, Palo Alto, CA) automated perimeter were ordered in space or time may exhibit autocorrelation or serial correlation,21 the Durbin-Watson d-statistic was computed from the residuals. Whenever a significant serial correlation was present (as evidenced by a significant d-statistic, P < 0.05), a distributed-lag model was fitted to the data. The residuals from the appropriate fit were examined to validate the other regression assumptions. At each time t, the regression coefficient Bt represented the slope of the profile in dB/degree and Dt, the mean sensitivity of the 24 locations in the profile (Dt = SDt/24). Dt was used as an index of the profile sensitivity and was preferable to using the intercept of the fitted line at e = 0, since in regression, the intercept is correlated to the slope. Figure 1 shows an example of a profile with the calculated statistics.

For each patient at time t (t = 4, 8, 12 . . . 72 months), the sensitivity of the locations in the 270° meridian, Dt (in dB) were regressed on eccentricity e (e = 2, 3, 4 . . . 25 degrees from fixation) using the ordinary least squares (OLS) technique.20 Since data ordered in space or time may exhibit autocorrelation or serial correlation,31 the Durbin-Watson d-statistic was computed from the residuals. Whenever a significant serial correlation was present (as evidenced by a significant d-statistic, P < 0.05), a distributed-lag model was fitted to the data. The residuals from the appropriate fit were examined to validate the other regression assumptions. At each time t, the regression coefficient Bt represented the slope of the profile in dB/degree and Dt, the mean sensitivity of the 24 locations in the profile (Dt = SDt/24). Dt was used as an index of the profile sensitivity and was preferable to using the intercept of the fitted line at e = 0, since in regression, the intercept is correlated to the slope. Figure 1 shows an example of a profile with the calculated statistics.

For each patient the sensitivity at location e, De was regressed on t in months. As above, an OLS or a
Fig. 1. Differential light sensitivities (D) at 2° to 25° eccentricity (e) along the 270° meridian at the sixth visit (t = 24 months) of an untreated patient. Ordinary least squares regression produced the equation: \(D_{24} = 20.18 - 0.383e\) whose residuals were not serially correlated \((P > 0.2)\). The profile sensitivity \(D_{24}\) was 15.00 dB and the slope \(B_{24}\) was 0.383 dB/degree.

A distributed-lag model was fitted. When the F-value for the regression was significant \((P < 0.05)\), the sensitivity at \(e\) “decreased” with time if the regression coefficient was negative and “increased” with time if the regression coefficient was positive. If the regression coefficient was not significantly different from 0 \((P > 0.05)\), then the sensitivity at \(e\) was “stable.” For each location, the standard deviation of \(D_e\), \(s(D_e)\), was computed. Figure 2 shows an example of \(D_e\) over time with the calculated statistics.

For each patient, the mean \(s(D_e)\) of the 24 locations, SD and the standard deviation of \(s(D_e)\), \(Ss(D_e)\) were computed. These variables are indices of the mean variability and the standard deviation of the variability in the sensitivity of the 24 locations.

In order to note changes in either the profile sensitivity or the slope (i.e., flattening or steepening) with time, \(D\) and \(B\) were regressed on \(t\) for each patient using the methods described above.

Analysis of covariance was carried out for the variables \(D\), \(B\) and IOP. The variables of the two groups could then be compared by adjusting for the components of variance described below. The following model was used:

\[
Y_{ijk} = \mu + \xi_i + \beta t_{(i)} + \gamma t^2_{(i)} + (g \times t)_{ijk} + (g \times t^2)_{ijk} + (p \times t)_{ijk} + (p \times t^2)_{ijk} + E_{ijk} (1)
\]

where \(Y_{ijk}\) is the dependent variable \(D\), \(B\) or IOP of the group \(i\), patient \(j\) at examination \(k\), \(\mu\) is the overall variable mean, \(\xi_i\) is the group effect, \(\beta\) and \(\gamma\) are the coefficients of linear and quadratic time, \((g \times t)_{ijk}\) and \((g \times t^2)_{ijk}\) are the \(g, t\) and \(g, t^2\) interactions and \((p \times t)_{ijk}\) and \((p \times t^2)_{ijk}\) are the \(p, t\) and \(p, t^2\) interactions. \(E_{ijk}\) is the error term.

Results

To date, 24 patients in the untreated group and 22 patients in the untreated group have completed 6 years of follow-up without optic disc or localized visual field changes. Twenty-two patients in the treated group and 25 patients in the untreated group were excluded from the study for visual field defects, disc changes or dangerously elevated IOP in one or both eyes. The number of patients excluded for field and disc changes are very similar in the two groups (Table 1). Eighteen patients in the treated group and 15 patients in the untreated group dropped out for the reasons outlined in Table 1. For the purpose of this in-
vestigation, one eye of each of the patients who completed the study was selected for the analysis.

The two groups were not significantly different in age, untreated IOP and visual acuity (transformed to the logarithm of the minimum angle of resolution, logMAR, for parametric analysis), blood pressure or pulse rate prior to commencing the study (Table 2).

The group distributions of the number of locations where the sensitivity was shown to decrease (Fig. 3a) and where the sensitivity remained stable (Fig. 3c) were similar. There appear, however, to be a greater number of sensitivity increases in the treated group than in the untreated group (upper quartiles are 4.50 and 1.00 locations respectively, Fig. 3b). The Mann-Whitney U-test was used to compare the two distributions in the three cases. No statistically significant differences were found in the number of sensitivity decreases (P = 0.193), sensitivity increases (P = 0.540) or in the number of stable locations (P = 0.412).

The distribution of the mean variability of the sensitivity in the 24 locations, SD, was similar in the two groups (medians were 1.48 dB in the treated group and 1.59 dB in the untreated group, Fig. 4a) and the Mann-Whitney test did not show a significant group difference (medians were 0.360 dB in the treated group and 0.410 dB in the untreated group, Fig. 4b). This was confirmed by the Mann-Whitney test (P = 0.349).

The regression of the profile sensitivity (D) on time and the slope of the profile (B) on time produced five types or modes of relationships. Mode 1 demonstrated a positive linear relationship with time (ie, D or B increased with time); mode 2, a negative linear relationship; mode 3, a quadratic relationship with a maximum (ie, D or B increased, peaked and then decreased with time); mode 4, a quadratic relationship with a minimum (ie, D or B decreased, troughed and then increased with time) and mode 5 showed no relationship between D or B and time. Modes 1 to 4

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**Table 2. Patient parameters at the start of the study**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treated group (n = 24)</th>
<th>Untreated group (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.54 ± 10.46</td>
<td>58.55 ± 7.00</td>
</tr>
<tr>
<td>IOP (mm Hg)</td>
<td>25.89 ± 2.95</td>
<td>25.86 ± 2.85</td>
</tr>
<tr>
<td>LogMAR (min arc)</td>
<td>0.0516 ± 0.141</td>
<td>0.0544 ± 0.140</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>139.42 ± 24.80</td>
<td>145.91 ± 22.97</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>81.58 ± 9.92</td>
<td>82.05 ± 9.21</td>
</tr>
<tr>
<td>Pulse (beats/min)</td>
<td>73.54 ± 7.44</td>
<td>75.69 ± 9.28</td>
</tr>
</tbody>
</table>

The values given are the mean ± standard deviation. F- and t-tests showed no significant difference in the variance (P > 0.05) and the means (P > 0.25) of the two groups.

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Fig. 3. Cumulative frequency plots of the number of locations where the sensitivity was shown to decrease (a), increase (b) and remain stable (c) in the treated group (solid line) and the untreated group (broken line).
were significant at the 5% level and in cases where both the linear and quadratic models were significant, the model with the highest coefficient of determination \( R^2 \) was selected. The maxima and the minima of the quadratic models always occurred within the 6 year follow-up.

Eleven patients (46%) in the treated group and 12 patients (55%) in the untreated group showed a stable profile sensitivity over the study period (Table 3). Seventeen patients (71%) in the treated group and 17 patients (77%) in the untreated group showed a stable slope in the tested meridian over time. The data in Table 3 have only a descriptive purpose since, owing to the low frequencies in the majority of the cells, they cannot be analyzed statistically.  

An analysis of covariance was carried out using the model discussed previously. The results show that when the \( D \) data was pooled, there was no group, \( t \) or \( t^2 \) effect (Table 4), hence the profile sensitivity was not significantly different in the two groups and did not change in either group over the 6 years. The adjusted mean \( D \) were computed as 14.35 dB in the treated group and 14.74 dB in the untreated group. Similarly, when the B data were pooled, there was no group, \( t \) or \( t^2 \) effect. The adjusted mean B were \(-0.331\) dB/degree in the treated group and \(-0.339\) dB/degree in the untreated group. The IOP data shows a different pattern. The covariates, \( t \) and \( t^2 \) were significant, indicating that the pooled IOP data showed a quadratic relationship with time. The interaction terms \((g \times t)\) and \((g \times t^2)\) were not significant and therefore the IOP/time slopes of the two groups at any given time during the follow-up were parallel. As expected, the group effect was significant since the IOP was lowered by timolol in the treated group and resulted in a difference of 4.9 mm Hg in the IOP/time

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Mode 1</th>
<th>Mode 2</th>
<th>Mode 3</th>
<th>Mode 4</th>
<th>Mode 5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>( D )</td>
<td>Treated</td>
<td>1</td>
<td>4</td>
<td>7</td>
<td>1</td>
<td>11</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Untreated</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>12</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>2</td>
<td>9</td>
<td>10</td>
<td>2</td>
<td>23</td>
<td>46</td>
</tr>
<tr>
<td>( B )</td>
<td>Treated</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Untreated</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>34</td>
<td>46</td>
</tr>
</tbody>
</table>
curves of the two groups after adjusting for the significant effects in the model.

As an adjunct to the analysis of those completing the study, a similar form of analysis was undertaken in those patients who did not complete the study, but survived to at least the 40 month period. The 40 month mark was chosen because it would allow analysis over a fairly long period of time, at the same time allowing a reasonable number of patients, which would not have been possible had a longer time period been selected. There were 12 patients in the treated group and 12 patients in the untreated group. There was no significant group difference in the number of locations where the sensitivity was shown to decrease ($P = 0.131$), increase ($P = 0.381$) or remain stable ($P = 0.060$). The analysis of covariance showed that when D and B were the dependent variables, none of the factors shown in Table 4 were statistically significant ($P > 0.40$). In addition, no significant ($P > 0.50$) factors were found when those who completed and those who did not complete the study in either the treated group or untreated group were pooled.

Discussion

The understanding of the effects that IOP reduction has on the visual field is central not only to the management of open angle glaucoma, but also to our knowledge of the role of IOP in this disease. It has been suggested that medical or surgical reduction of IOP in patients with glaucomatous visual field damage reduces or halts further damage and in some cases even causes an improvement of the field. Artificial elevation of IOP in normal subjects has been demonstrated to produce a reduction in visual sensitivity.

Table 4. Significance of factors ($P$-values) from the analysis of covariance of the profile sensitivity (D), profile slope (B) and IOP

<table>
<thead>
<tr>
<th>Factor</th>
<th>D</th>
<th>B</th>
<th>IOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group (g)</td>
<td>0.103</td>
<td>0.861</td>
<td>0.000</td>
</tr>
<tr>
<td>Time (t)</td>
<td>0.454</td>
<td>0.925</td>
<td>0.000</td>
</tr>
<tr>
<td>$t^2$</td>
<td>0.121</td>
<td>0.346</td>
<td>0.000</td>
</tr>
<tr>
<td>$(g \times t)$</td>
<td>0.850</td>
<td>0.708</td>
<td>0.387</td>
</tr>
<tr>
<td>$(g \times t^2)$</td>
<td>0.694</td>
<td>0.608</td>
<td>0.514</td>
</tr>
</tbody>
</table>

The results of the present investigation have shown that the number of patients developing glaucomatous visual field and optic disc changes in the timolol-treated and untreated groups were remarkably similar, as was the number of patients dropping out. Since Table 1 contains patients with one or both eyes involved in the various categories, formal statistical analysis cannot be performed; however, this does not detract from the observation that the treated group did not contain a lower frequency of patients with field and disc changes. There was a greater number of untreated patients who required treatment on the basis of IOP alone.

In this investigation, we excluded those patients with localized field defects and acquired disc changes and then compared all surviving treated and untreated patients with regard to any subtle serial changes in the differential light sensitivity in order to study the effects of reducing IOP in glaucoma suspects who only have elevated IOP.

Over the 6 year study period, the sensitivity at the great majority of the tested locations in the surviving patients remained stable in both the treated and untreated groups. Some patients in both groups showed a small number of sensitivity decreases and fewer patients showed a smaller number of sensitivity increases. The analysis suggests that when examining the data in terms of the behavior of the sensitivity at specific locations over time, the differences between the two groups were not statistically significant.

There was no difference in the mean variability of the sensitivity (akin to the long-term fluctuation) or in the standard deviation of the variability in the test locations in the two groups. Direct comparisons with published long-term fluctuation values in normals, glaucoma suspects and glaucoma patients cannot be made due to the differences in computing the actual values and the testing methods. However, since the threshold fluctuation (both short- and long-term) or variability is greater in glaucoma suspects than in normals, and in turn greater in glaucoma patients than in suspects, and the fact that our two groups did not show a difference in variability, imply that both our groups were similar with regard to the level of normality or abnormality.

The results have shown that the patients exhibited different types or modes of behavior of the profile sensitivity and the profile slope with time. There appear to be small differences between the groups in the frequencies with which some of these modes occur (Table 2). Although in isolation these differences may seem significant, the comparisons cannot be made with the exclusion of the other modes of behavior with time. In spite of individuals exhibiting significant profile sensitivity or slope relationships with time, the overall data showed that the time effect was not statistically significant. The inference from this is that both groups had stable profile sensitivities and slopes with time. In addition, the differences in the adjusted means of the profile sensitivity and slope were not statistically significant.
As expected, timolol reduced the IOP in the treated group. It is interesting to observe that the IOP/time functions of the two groups were parallel, indicating that the IOP lowering effect of timolol was at a consistent level (4.9 mm Hg) throughout the follow-up. No relative change in profile sensitivity or slope occurred between the two groups. In any case, the differential light sensitivities were not affected by a change in the difference of IOP between the two groups. The behavior of the IOP in the two groups will be the topic of another paper.

The number of patients so far completing the 6 year study is relatively small, considering the initial number admitted to the study. A common statistical procedure carried out in studies when the sample is suspected to be small is the calculation of the power of the test used to reject or not reject a particular null hypothesis. This is a complex procedure when the underlying sample distribution of the tested variable is nonparametric; however, for parametric distributions, such as those of the profile sensitivity and profile slope, the power of the test can be calculated relatively easily. The power to detect a 1 dB difference in the overall adjusted mean profile sensitivity (from the analysis of covariance) in the two groups was approximately 72%, that is, with the sample distributions of the profile sensitivity in the treated and the untreated groups, a mean difference of as little as 1 dB, had it existed, would have been detected 72% of the time. The power to detect a mean 1.5 dB change was 97%. Similarly a 0.04 dB/degree steepening of the slope (translating to a 1 dB drop at 25° eccentricity) would have been detected 70% of the time. These power figures outline the high statistical confidence of the covariance tests which indicated no difference between the groups.

Analysis of the results of all patients surviving to at least the 40 month mark but failing to complete the study showed no group difference and therefore the pattern evidenced in the patients who completed the follow-up also seems present in those who did not. Since there was no evidence for a difference between those who completed the follow-up and those who did not, in either the treated or untreated group, there appears to be no selection of patients who proceeded to complete the follow-up. The lack of selection shows that the localized field loss or disc change that led to the exclusion of a patient was not preceded by a deterioration in profile sensitivity or a change in profile slope. This was the case whether the patient was treated or untreated. Since similar serial differential light sensitivity data are not easily available for normotensive patients without pathological discs or fields, we cannot compare the present findings with those of individuals who are essentially normal. With the present analysis we cannot accurately compare the incidence of field and disc changes in the treated and untreated glaucoma suspects and thereby predict if pressure reduction with timolol in those who have only elevated IOP as the risk factor will prevent or delay the onset of glaucomatous damage. It may be possible to shed some light on these questions once the ongoing study has been terminated and the findings evaluated as a whole. The lack of statistical significance in the parametric results between the two groups does not suggest that biologically different changes had not occurred in the two groups. Nevertheless, the absence of even consistent trends between the groups suggests that the differential light sensitivity in those patients who have not developed localized visual field damage and whose IOP is reduced with timolol over a 6 year period behaves no differently from that in those patients without treatment.

Key words: glaucoma suspect, timolol, automated perimetry, intraocular pressure (IOP), IOP reduction

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References

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