**SCIENTIFIC REPORT**

Contrast sensitivity improves after brimonidine therapy in primary open angle glaucoma: a case for neuroprotection

D W Evans, S L Hosking, D Gherghel, J D Bartlett

Aims: To determine the visual outcome following initiation of brimonidine therapy in glaucoma.

Methods: 16 newly diagnosed previously untreated glaucoma patients were randomly assigned to either timolol 0.5% or brimonidine 0.2%. Visual acuity, contrast sensitivity (CS), visual fields, intraocular pressure (IOP), blood pressure, and heart rate were evaluated at baseline and after 3 months.

Results: IOP reduction was similar for both groups (p<0.05). Brimonidine improved CS; in the right eye at 6 and 12 cpd (p=0.043, p=0.017); in the left eye at 3 and 12 cpd (p=0.044, p=0.046). Timolol reduced CS at 18 cpd in the right eye (p=0.041). There was no change in any other measured parameters.

Conclusion: Glaucoma patients exhibit improved CS on initiation of brimonidine therapy.

Increased intraocular pressure (IOP) is the risk factor most often associated with glaucoma; however, there is strong evidence to suggest that there are pressure independent mechanisms associated with the development of the disease.

The optic nerve damage in glaucoma affects contrast sensitivity to a greater extent than visual acuity. It has also been shown that contrast sensitivity improves on initiation of ocular hypotensive therapy, either through the use of β blockers or following surgical reduction of IOP.

There is accumulating evidence that IOP lowering augmented effects, two practice trials were conducted before the first baseline measurement and one before each subsequent visit.

Patients were randomised into one of two treatment groups with (a) timolol gel 0.5%, or (b) brimonidine 0.2%. Patients and investigators were masked to the treatment condition. For each patient, two bottles of the drug were provided, one for the morning and one for the evening dosage. For the timolol treatment group, the evening dosage was a vehicle placebo. Patients returned after 3 months to be tested for IOP, CS, VF, BP, and HR.

The pre-treatment and post-treatment differences in IOP, CS, VF, BP, and HR for the two study groups were assessed.

**Table 1 Baseline characteristics for the study samples**

<table>
<thead>
<tr>
<th></th>
<th>Brimonidine (mean (SD))</th>
<th>Timolol (mean (SD))</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.86 (8.59)</td>
<td>60.11 (10.91)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Visual acuity RE (logMAR)</td>
<td>0.01 (0.06)</td>
<td>0.07 (0.06)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Visual acuity LE (logMAR)</td>
<td>0.003 (0.07)</td>
<td>0.09 (0.08)</td>
<td>0.0443</td>
</tr>
<tr>
<td>IOP RE (mm Hg)</td>
<td>22.35 (6.10)</td>
<td>23.35 (5.69)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>IOP LE (mm Hg)</td>
<td>22.35 (6.26)</td>
<td>22.35 (5.16)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>MD RE (dB)</td>
<td>-4.15 (3.78)</td>
<td>-6.80 (4.48)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>MD LE (dB)</td>
<td>-5.82 (4.04)</td>
<td>-6.96 (8.78)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>136.43 (12.49)</td>
<td>142.55 (12.50)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>86.00 (7.39)</td>
<td>84.89 (8.13)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>102.81 (7.94)</td>
<td>104.11 (8.25)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>76.43 (11.54)</td>
<td>77.63 (14.00)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

BP = blood pressure, IOP = intraocular pressure, MD = visual field mean defect, RE = right eye, LE = left eye.
using repeated measures analysis of variance (REANOVA). A p value of less than 0.05 was considered statistically significant.

RESULTS
At baseline, the groups were similar for age, IOP, VF mean deviation, systemic BP, and HR; visual acuity was slightly worse in the left eye of the timolol treated group (p = 0.044) (Table 1).

The IOP reduction after 3 months of treatment was statistically significant and similar in both study groups (Fig 1).

After 3 months of treatment there was a significant improvement in contrast sensitivity in the brimonidine treated group; for 6 and 12 cycles/degree in the right eye (p = 0.043; p = 0.017 respectively), and for the 3 and 12 cycles/degree in the left eye (p = 0.044; p = 0.046 respectively). In contrast, the timolol treated group demonstrated a significant decrease in contrast sensitivity in the RE at 18 cycles/degree (p = 0.041) and no other change. These effects are summarised in Figure 1. There was no change in VF, BP, or HR after 3 months of treatment (p > 0.05).

DISCUSSION
In this study, contrast sensitivity improved after 3 months of treatment with brimonidine 0.2%, while timolol therapy resulted in no improvement but some deterioration in CS. The IOP lowering effects of the two drugs were similar, suggesting an IOP independent mechanism for the visual outcome.

During a disease process, subpopulations of cells may be dead, dying, or healthy depending on the degree and duration of the disease. It is likely that improvements in function such as those reported here, and previously, could be the result of recovery of function in dying cells that return to a healthier status following treatment. This is not to suggest that improvements are progressive, but most likely a stepped response to the onset of therapy.

The density of ganglion cells is around 70-fold greater in the central 3 degrees than that at 20 degrees eccentricity where a nasal step VF defect typically appears. This high density of retinal ganglion cells in central vision may result in oversampling or visual redundancy, during most visual function investigations and a relatively late detection of defects in the central visual field. Contrast sensitivity is a more sensitive test enabling subtle defects or improvements to be detected centrally in the early stages of disease. Any visual improvement in the neurological functioning of the retinal ganglion cells would be demonstrated only where test variability was extremely low, such as in central vision. Investigations of visual function that combine low variability and a low sampling density are most likely to demonstrate any subtle functional improvements, as shown in this study.

Brimonidine has a known neuroprotective effect, probably linked to the alpha-2 receptor and its signalling pathway. Alpha-2 receptors are present in the retina, and alpha-2 agonists such as brimonidine have exhibited neuroprotective properties following crush injury, pressure induced retinal ischaemia and chronic elevation of intraocular pressure. Recently, WoldeMussie, et al demonstrated a dose dependent reduction in progression of retinal ganglion cell loss following administration of brimonidine which was not present using timolol, and not linked to IOP lowering effects.

Treatment related perfusion changes unrelated to IOP affect contrast sensitivity. Blood velocity in the ophthalmic artery is highly correlated with changes in contrast sensitivity in normal tension glaucoma patients following treatment with nifedipine. However, no such association has been found in POAG patients treated with either timolol

Figure 1 Graphs showing the baseline findings and 3 month post-treatment data for patients treated with brimonidine 0.2% (solid lines) and timolol 0.5% (broken lines) for the right eye (above) and left eye (below). Data shown (from left to right) include the IOP (mm Hg), and CS at 3, 6, 12, and 18 cpd. Where significant change occurred the p value is shown; NS = not significant.
or brimonidine and an alternative, possibly neuroprotective, mechanism for the improvement in contrast sensitivity following treatment with brimonidine should be considered.

These data clearly demonstrate that CS improves on initiation of brimonidine therapy in glaucoma. This finding does not appear to be related to IOP lowering effects but rather may be linked to the neuroprotective capabilities of this therapy.

Authors’ affiliations
D W Evans, School of Optometry, University of Alabama at Birmingham, Birmingham, AL, USA
S L Hosking, D Gherghel, Neuroscience Research Institute, Aston University, Aston Triangle, Birmingham B4 7ET, UK
J D Bartlett, School of Optometry, University of Alabama at Birmingham, and Department of Pharmacology and Toxicology, School of Medicine, University of Alabama, Birmingham, AL, USA

REFERENCES

16 Evans D, Harris A, Cantor LB. Primary open-angle glaucoma patients characterized by ocular vasospasm demonstrate a different ocular vascular response to timolol versus beta-adrenergic J Ocul Pharmacol Ther 1999;15:479–87.