Proliferative diabetic retinopathy: treatment with xenon-arc photocoagulation

Interim report of multicentre randomised controlled trial

British Medical Journal, 1977, 1, 739-741

Summary
One hundred patients with symmetrical proliferative diabetic retinopathy had one eye randomly chosen for treatment with xenon-arc photocoagulation while the other was left untreated as a control. Patients were subdivided into those with new vessels on both optic discs and those with only peripheral new vessels. In patients with new vessels on the optic discs the vision of the untreated eye deteriorated more than that of the treated eyes and the difference in deterioration was significant after one, two, and three years. There was no such difference in patients who had only peripheral new vessels.

Eighteen patients had become blind in one or both eyes by the last assessment, but only one patient became blind in the treated eye without concomitant blindness in the untreated eye. Thirteen were blind only in the untreated eye. Both photographic and ophthalmoscopic examinations showed that new vessels on the disc regressed more in the treated eyes than in the untreated ones. As some forms of diabetic retinopathy are now treatable, early diagnosis and evaluation is increasingly important.

Introduction
In 1975 the first interim report of the British Multicentre Photocoagulation Trial reported that photocoagulation produced significant benefits in the treatment of diabetic maculopathy. We report here the result of the multicentre study as it applies to proliferative diabetic retinopathy. Proliferative retinopathy is characterised by abnormal "new" vessels that may arise from the optic disc or the peripheral retina. In the later stages of the disease the vessels may be associated with varying amounts of fibrous tissue. Loss of vision is caused by recurrent vitreous haemorrhage, which may become organised by fibrosis or by retinal detachment. It is the commonest cause of blindness between the ages of 30 and 65 years.

A multicentre study supported by the National Institutes of Health is also in progress in the United States. A preliminary report of that study indicated that both xenon-arc and argon laser photocoagulation conferred significant benefit on the treated eye, especially if there had been vitreous haemorrhage. We studied the effects of xenon-arc photocoagulation in patients with varying degrees of proliferative retinopathy.

Patients and methods
Patients who presented at hospital diabetic clinics with visual symptoms and those found on screening to have proliferative diabetic retinopathy were recruited to the trial. They were admitted only if both eyes were similarly affected and if they gave their informed consent. The eyes were considered similar when visual acuity did not differ by more than two lines of the Snellen test type and when observable retinopathy features did not differ by more than two Hammersmith Hospital grades.

Patients were excluded from the trial if: (a) they were unlikely to survive one year; (b) there was intercurrent disease of the eyes or visual pathways likely to affect visual acuity or clarity of the media during the period of observation; (c) there was more than a wisp of fibrous retinitis proliferans in the fundus; (d) there was macular scarring; (e) there was detachment or retinoschisis in the temporal half of the fundus; (f) the media were not clear enough for fundus photography and impeded central vision.

Randomisation—The co-ordinating centre provided each participating centre with a set of sealed numbered envelopes. As each new patient was entered into the trial, the next envelope in the set was opened. The forms inside the envelope indicated (from a system of random allocation) whether the treatment should be applied to the right or the left eye of the patient. Each patient had only one eye treated, the other acting as a control.

Treatment—All the treated eyes underwent xenon-arc photocoagulation, most of them under local (retrobulbar) anaesthesia.
The apparatus used was the Zeiss (Oberkochen) or the O'Malley light coagulator. The mode of treatment was by attempted coagulation of all flat retinal vessels except those lying too near the macular or over the papillomacular bundle. All but two centres (King's College Hospital and Nottingham Eye Hospital) also used "scattered" coagulopathy, applying burns to all visible "dot" and "blot" lesions outside the temporal vessels. More recently large areas of non-perfused retina were treated diffusely in eyes that had new vessels on the disc. Where flat new vessels arose from the nasal side of the disc photocoagulation was carried to its edge. Up to 500 applications were used at a treatment session, and treatment was given as often as new vessels were detected. Most patients had more than one treatment session.

Data collected—The best corrected visual acuity was recorded before treatment and yearly thereafter. The photographs of the disc and macula, taken each year, were centrally graded by the co-ordinator and by an unbiased specially trained nurse-technician using the Hammersmith Hospital grading system. Clinical data on the eyes, details of medical management, diabetic control, and general health were also recorded. Changes in visual acuity and the grading value of new vessels on the disc are reported here; a more detailed analysis will appear in the final report of the trial.

Analysis—The patients were analysed in three groups: (a) the overall group containing all the patients; (b) the subgroup of patients who had new vessels on both optic discs initially (group 1); and (c) the subgroup of patients who had new vessels on neither optic disc initially (group 2). Results from the first, second, and third annual assessments were compared with the results of the initial assessment. Visual acuities were transformed into a numerical scale. The paired t test was used to compare the difference in deterioration of visual acuity in the treated and untreated eyes. Eyes were considered blind if the visual acuity was less than 6/60 on the Snellen test. Photographs of the optic disc were graded for new vessels, and the grading values of the photographs taken at one, two, and three years were compared with those of the initial photographs. When the grading value became worse or remained unchanged the values were accepted. Improvement was considered valid only if the fibrous tissue on the disc was minimal (grade 1) or absent. Disappearance of new vessels was considered genuine only if they were also absent ophthalmoscopically. If the initial or subsequent photographs were too poor for grading they were classed as "unknown." If the photographs were poor because of vitreous haemorrhage or vitreous fibrosis they were classed as "unassessable." All centres that withdrew patients so that they could treat the control eye were excluded from this analysis.

Results

The overall group consisted of 100 patients who had been followed for at least a year. Fifty-eight had been followed for at least two years, and 23 of the 58 had been followed for at least three years. Group 1 (patients with new vessels on the disc) consisted of 47 patients who had been followed for at least a year, 29 followed for at least two years, and 16 followed for at least three years. Group 2 (peripheral new vessels only) consisted of 55 patients who had been followed for at least a year, 25 followed for two years, and seven followed for three years. There were eight patients who could not be classified into either group 1 or group 2.

Eighty per cent of patients in both groups were aged 19-55 years. Most patients had been dependent on insulin from the onset of diabetes, and the mean duration of diabetes was 16-3 years (range 1-51 years). There was no significant difference between groups 1 and 2 in terms of the duration of diabetes.

Visual Acuity

Overall group—As would be expected after randomisation, there was little difference between the initial visual acuities of the treated and untreated eyes. The difference in deterioration between the treated and untreated eyes was significant after three years (P < 0.02) (table I). The mean visual acuity of the treated eyes was better than that of the untreated eyes after one, two, and three years.

Group 1—At each assessment the treated eyes had deteriorated less than the untreated ones; this difference was significant at one year (P < 0.05), two years (P < 0.02), and three years (P < 0.02) (table I). The mean visual acuity of the treated eyes was better than that of the untreated eyes at each annual assessment (see figure).

Table I—Difference in deterioration between untreated and treated eyes in whole group

<table>
<thead>
<tr>
<th>Follow-up (years)</th>
<th>No of cases</th>
<th>Mean difference in deterioration (SD)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>0.52 ± 0.27</td>
<td>1.94</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>0.71 ± 0.36</td>
<td>2.04</td>
<td>0.81</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>0.80 ± 0.43</td>
<td>2.04</td>
<td>2.52</td>
</tr>
</tbody>
</table>

*At one-year follow-up, for example, this difference was: \( \text{VA}_{t}-\text{VA}_{u} \), where \( \text{VA} \) = visual acuity, \( t \) = untreated, \( u \) = initial value, and 1 = one-year value. Values were translated into a numerical scale.

Table II—Difference in deterioration between untreated and treated eyes in group 1

<table>
<thead>
<tr>
<th>Follow-up (years)</th>
<th>No of cases</th>
<th>Mean difference in deterioration (SD)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47</td>
<td>0.69 ± 0.28</td>
<td>2.77</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>0.81 ± 0.29</td>
<td>2.67</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>0.82 ± 0.30</td>
<td>2.69</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

*See footnote to table I for explanation.

Table III—Difference in deterioration between untreated and treated eyes in group 2

<table>
<thead>
<tr>
<th>Follow-up (years)</th>
<th>No of cases</th>
<th>Mean difference in deterioration (SD)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>0.64 ± 0.29</td>
<td>0.15</td>
<td>Not significant</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>0.65 ± 0.30</td>
<td>0.38</td>
<td>**</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>0.65 ± 0.29</td>
<td>0.29</td>
<td>**</td>
</tr>
</tbody>
</table>

*See footnote to table I for explanation.

Blindness

Out of the 100 patients followed for at least one year 18 had become blind in one or both eyes by the last assessment. Four were blind in both eyes, one was blind in the treated eye only, and the other 13 were blind only in the untreated eye. This difference between the treated and untreated eyes was significant (P < 0.04). Of the 98
patients followed for at least two years 11 were blind in one or both eyes for at least two consecutive assessments. Of these, three were blind in both eyes and eight were blind in the untreated eye only. Again, the difference between the treated and the untreated eyes was significant (P < 0.02).

The commonest cause of blindness was vitreous haemorrhage, followed by traction retinal detachment and rubeotic glaucoma. All eyes that became blind either had new vessels on the disc at the initial assessment or had developed them before the onset of blindness.

PHOTOGRAPHIC AND CLINICAL ASSESSMENT OF DISC NEW VESSELS

Group 1—Table IV shows the number of eyes in which the number of new vessels on the disc had increased, remained unchanged, or diminished. More treated eyes than untreated ones showed an improvement in grading value, and the difference was significant (P < 0.01 at one and two years). More of the untreated eyes became unassessable because of unclear media, and the proportion increased with time.

![Table IV—Photographic grading for group 1](image)

<table>
<thead>
<tr>
<th></th>
<th>Initial v 1 year</th>
<th>Initial v 2 years</th>
<th>Initial v 3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treated</td>
<td>Untreated</td>
<td>Treated</td>
</tr>
<tr>
<td>Worse</td>
<td>10</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>Unchanged</td>
<td>9</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Improved</td>
<td>13</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Total assessed</td>
<td>32</td>
<td>29</td>
<td>21</td>
</tr>
</tbody>
</table>

The American study shows that fewer patients had no new vessels on the disc but had suffered a vitreous haemorrhage before admission to the trial did significantly better with treatment than without. Therefore our findings should not preclude patients with peripheral new vessels from having treatment if there are other bad prognostic signs.

Photographic analysis also showed that new vessels on the disc regressed in the treated eyes, and in some they even disappeared. Since xenon-arc photocoagulation cannot remove new vessels from the disc entirely, both because of the absence of pigment that absorbs light and for fear of damage to the papillomacular bundle, the beneficial effect does not depend on complete destruction of new vessels. The argon laser is potentially capable of destroying new vessels on the disc because of its optical properties. In the American study, however, the results in eyes treated by xenon-arc photocoagulation and by argon laser were not significantly different. In fact, eyes treated by xenon-arc photocoagulation did marginally better, although the field loss was greater than in those treated by the argon laser. A possible explanation of this response to treatment is that ablation of peripheral ischaemic retina had removed the stimulus for progression of the disease. These findings therefore lend support to the hypothesis of Ashton* and Wise** that the stimulus to new vessel proliferation may have come from ischaemic retina. In our study the one treated eye that became blind without concomitant blindness in the untreated eye had had only limited photocoagulation treatment, which was confined to areas of new vessel formation.

Our findings and those already published emphasise with new urgency the need for early diagnosis and evaluation of diabetic retinopathy by both physicians and ophthalmologists, since some forms of this condition are now treatable. Treatment should be timely and adequate with systematic follow-up and additional treatment when necessary. The treatment is potentially hazardous so the technique is important. Inadequate treatment or delay in its application may prejudice the prognosis for an eye that may pass quickly from a treatable to an irreversible phase of retinopathy.

We thank all fellows and colleagues who have contributed to the assessment and management of patients in the last six years. This study was supported by the Scientific Section of the British Diabetic Association and the Welcome Trust.

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References

1 Multicentre Controlled Study, Lancet, 1975, 2, 1110.
8 Caird, F E, Burdett, A P, and Draper, G J, Diabetes, 1968, 17, 121.

(Accepted 6 January 1977)