Xenon arc photocoagulation for the treatment of diabetic maculopathy

Interim report of a multicentre controlled clinical study

C. TOWNSEND, J. BAILEY, AND E. KOHNER

From the 1Hammersmith Hospital, London, and the 2London School of Hygiene and Tropical Medicine

SUMMARY The results of a randomised controlled clinical study in the treatment of diabetic maculopathy are reported. Ninety-nine patients with two similarly affected eyes had one—chosen by random procedure—treated, while the other was left as an untreated control. Visual acuity was maintained in the treated eyes, while it deteriorated in the untreated eyes, reaching over 2 lines difference after 4 years. The difference in deterioration was significantly less in treated than in untreated eyes at each assessment. After 4 years the difference between the 2 eyes was greatest in those with initially good vision. There was no difference in visual acuity in patients whose initial vision was less than 6/36. Only 9 treated but 25 control eyes lost vision to blindness (P < 0.001). It is concluded that maculopathy is a treatable form of diabetic retinopathy if treated before severe visual loss occurs.

In diabetic retinopathy loss of visual acuity can result either from the sequelae of proliferative retinopathy or from maculopathy. During the last few years reports have been published showing the effectiveness of photocoagulation for proliferative retinopathy, especially when the optic disc is involved. There is much less evidence about the efficacy of treatment in diabetic maculopathy. There are only 3 previous reports on randomised controlled studies of diabetic maculopathy. None of these followed up the patients for longer than 3 years. In our present paper we are reporting the results of treatment for diabetic maculopathy with xenon arc photocoagulation in the British Multicentre Study at a time when an important number of patients have been followed up for 5 years.

Patients and methods

These were described in detail in 1975. A summary is given below.

Definitions

Macula was defined as the fovea and the area immediately surrounding it extending to approximately 1 disc diameter from the centre of the fovea in all directions.

Maculopathy was defined as a visual acuity of 6/9 or less on the Snellen test type in the presence of macular oedema in association with haemorrhages, microaneurysms, and exudates. Patients with a visual acuity better than 6/9 were included if ophthalmoscopically hard exudates were seen to encroach on the macula.

Patients

Patients were included in the trial if they had diabetic maculopathy of a similar severity in both eyes. Similarity was defined as a visual acuity within 2 lines of the Snellen test type between the 2 eyes and clinically observable features of retinopathy of approximately the same severity (within 2 Hammersmith Hospital Grades).

Patients were excluded from the trial if: (1) They
were unlikely to survive for 1 year; (2) 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; (3) there was more than a wisp of fibrous retinitis proliferans in the fundus; (4) there was macular scarring; (5) there was detachment or retinoschisis in the temporal half of the fundus; (6) the media were not clear enough for fundus photography and unimpeded central vision.

The presence of early new vessels did not automatically exclude a patient from the trial, but new vessels if present had to be present in both eyes for the patient to be included. This combination of proliferative retinopathy and maculopathy was seen in 13 out of 99 patients.

**METHODS**

*Randomisation.* Patients whose eyes were suitable for the trial were entered after obtaining informed consent. One eye chosen by random procedure was allocated for treatment while the other remained untreated. Randomisation was carried out by the co-ordinating centre. Each treating centre was provided with sealed envelopes containing the randomisation; the envelopes were numbered and opened in strict numerical order.

*Treatment.* The eye chosen for treatment had xenon arc photocoagulation, usually under local (retrobulbar) anaesthesia but occasionally under general anaesthesia. The apparatus used was the Zeiss (Oberkochen) or the O'Malley Log 2 Light Coagulator. Treatment was given according to the clinical judgment of the ophthalmologist in charge. The treated eye could be treated any number of times. Neither the number, the site, the intensity of, nor the area covered by the burns used was specified. Once an eye had been selected for treatment the mode and number of treatments was left to the discretion of the ophthalmologist no matter what lesion, whether new vessel or maculopathy. In general the treatment given was focal to areas of microvascular abnormalities between the superior and inferior temporal vessels, including the area lateral to the macula. Focal treatment was also used initially for new vessels when present. Panretinal photocoagulation for proliferative lesions was carried out if patients developed new vessels on the optic disc in the treated eye. There were 9 such eyes. Control eyes were never treated unless new vessels developed on the optic disc; in that case the patient was withdrawn from the trial.

*Data collected.* The corrected visual acuity was recorded at the beginning and at yearly intervals thereafter. When possible the person testing was not involved in the treatment. This was achieved in at least 80 of the patients. At each annual assessment the disc and macula were photographed and were graded by the secretary and co-ordinator using the Hammersmith Hospital Grading System. Details of the patients' general health, their management by the physicians, and their diabetic control were also recorded.

This paper reports only changes in the visual acuity. A full analysis of other features, including mortality and medical data, will appear in the final report of this trial. Only patients followed up for at least 1 year are included in this study.

**ANALYSIS**

The data were analysed on the CDC 6600 computer at the University of London Computer Centre. For the purpose of the analysis the visual acuities were coded from 1 to 10 (1 for 6/6, 2 for 6/9, etc.). An eye was considered to be worse if the visual acuity worsened by 1 line or more on the Snellen chart. Similarly, an eye was considered to have improved if the visual acuity improved by 1 line or more.

Two tests were done for each yearly follow-up to compare the behaviour of the treated and untreated eyes. Firstly, for each patient the deterioration (measured by number of lines) in each eye since the initial assessment was calculated, and a paired *t* test was performed on these changes. For example, at the 1-year follow-up the difference in deterioration of vision between treated and untreated eye, *d*, was calculated as *(AVui − AVuo) − (VAti − VAt0)* where *VA* = visual acuity and *u* and *t* stand for untreated and treated eyes; *i* and *o* stand for initial and one year values. Secondly, McNemar's test was used to compare those in whom only the treated eye was worse with the patients in whom only the untreated eye was worse. Another test was done on those patients who were blind at the last 2 annual assessments. For these patients McNemar's test was again used to compare the number of patients who were blind only in the treated eye with those who were blind only in the untreated eye.

The mean visual acuity for treated eyes and untreated eyes was also calculated for each assessment. Plots were also made of initial visual acuity against annual visual acuity.

**Results**

A total of 99 patients were followed up for at least 1 year. Of these, 81 were followed up for at least 2 years, 71 for at least 3 years, 35 for at least 4 years, and 23 for 5 years. The mean age of entry to the trial was 58.4 years (range 20–76). Known duration of diabetes was 8.8 years (range 0–34).
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**Visual Acuities**

Fig. 1 (a–c) shows the mean yearly visual acuities for the patients followed up for 1 to 5 years. This figure shows that initially, and at 1 year, the visual acuities of the treated and untreated eyes were similar. At 2 years the difference in visual acuity was half a line in favour of treatment. At 3 years the difference increased to almost 1 line and at 4 and 5 years to 2 lines in favour of treatment. When all eyes were considered, the vision of the treated eyes deteriorated significantly less than the vision of the untreated eyes at each yearly interval (Table 1). In the group with mean visual acuities of 6/12, 6/18, and 6/24 the difference in deterioration in visual acuity was less in the treated eyes than the untreated ones, reaching significant levels for the first 4 years (Table 2). The results for the fifth assessment may be significant when a greater number have reached this stage. There were only 19 patients with an initial visual acuity of 6/9 or better, and only 6 of these have been followed up for the full 5 years. It is in this group that the greatest difference in deterioration was seen, amounting to over 4 lines difference at 4 and 5 years in favour of treatment (Table 3). In the 19 patients with an initial visual acuity of 6/36 or worse there was at no time a
statistical significance in difference in deterioration between the treated and the untreated eyes. After 2 years there were 20 patients for whom the untreated eye was worse when the treated eye improved or remained unchanged, but only 6 patients for whom only the treated eye was worse (Table 4). McNemar's test gave $\chi^2=6.5$ ($P<0.05$). Similar results were obtained after 3 years ($P<0.001$), 4 years ($P<0.01$), and 5 years ($P<0.01$).

### Table 1  Difference in deterioration of vision all patients

<table>
<thead>
<tr>
<th>Time (yr)</th>
<th>N</th>
<th>$d$</th>
<th>SE(d)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>99</td>
<td>0.535</td>
<td>0.180</td>
<td>3.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>2</td>
<td>81</td>
<td>0.667</td>
<td>0.211</td>
<td>3.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>3</td>
<td>71</td>
<td>1.042</td>
<td>0.297</td>
<td>3.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4</td>
<td>35</td>
<td>2.000</td>
<td>0.458</td>
<td>4.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>2.130</td>
<td>0.570</td>
<td>3.7</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

N = number of patients. $d$ = Difference in deterioration of vision between treated and untreated eyes. SE = standard error.

### Table 2  Difference in deterioration of vision patients with mean initial vision 6/12–6/24

<table>
<thead>
<tr>
<th>Time (yr)</th>
<th>N</th>
<th>$d$</th>
<th>SE(d)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>0.689</td>
<td>0.226</td>
<td>3.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>2</td>
<td>49</td>
<td>0.694</td>
<td>0.248</td>
<td>2.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>1.273</td>
<td>0.376</td>
<td>3.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>1.762</td>
<td>0.585</td>
<td>3.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>1.385</td>
<td>0.646</td>
<td>2.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

Annotation as in Table 1.
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A graphical representation of the change in visual acuity of each individual eye was made by plotting the visual acuity from each annual assessment against the initial vision. Figs. 2 and 3 are such plots at 4 and 5 years respectively when the changes were largest. Both these figures illustrate that considerably fewer of the treated eyes deteriorated than did the untreated eyes, and this is particularly noticeable in eyes with initially good visual acuity of 6/6–6/12.

Fig. 2 Initial and 4-year visual acuity of 35 patients followed up for this time. Each eye is represented by a dot. Diagonal line represents no change. CF = count fingers. HM = hand movements. PL = perception of light. NPL = no perception of light.

Fig. 3 Initial and 5-year visual acuity in 23 patients followed up for 5 years. Annotation as in Fig. 2.
Table 5 Causes of visual loss

<table>
<thead>
<tr>
<th></th>
<th>Treated</th>
<th>Untreated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hard exudate plaque and scar</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Gross macular oedema</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Complications of new vessels</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>25</td>
</tr>
</tbody>
</table>

**Blindness**

In this study blindness was defined as a visual acuity of 6/60 or worse for 2 consecutive yearly assessments including the latest one. Of 81 patients followed up for at least 2 years the following were blind for the last two assessments: 7 in both eyes, 2 in the treated eye only, and 18 in the untreated eye only (P<0.001 for McNemar's test). A further 3 treated and 3 untreated eyes were blind at 1 stage but improved to 6/36 or better by the latest assessment, and are therefore not included among the blind.

The causes of visual loss are summarised in Table 5. The initial causes of visual loss were mostly the development of hard exudate plaque in the fovea, or worsening of macular oedema. This occurred in 6 treated eyes and 20 untreated eyes. In 1 treated eye the extension of the hard exudate into the fovea occurred after the first 3 days following treatment and was therefore attributed to the treatment. New vessels and their complications, vitreous haemorrhage, fibrous tissue formation, and thrombotic glaucoma were the primary cause of visual loss in 5 untreated and 3 treated eyes. Three of the untreated eyes which became blind had new vessels present in the affected eye at the time of entry into the study. Vitreous haemorrhage caused severe visual loss (worse than 6/60) as a secondary cause in 6 untreated and 3 treated eyes. These eyes were already blind from maculopathy but retained navigational vision until the development of the haemorrhage. In 1 treated eye vitreous haemorrhage occurred after cataract extraction, and in another eye new vessels were not seen on any previous examination, probably because of lens opacities. Of the blind eyes 3 treated and 6 untreated eyes were already 6/60 at the initial assessment. Five treated eyes which had a visual acuity of 6/60 at entry into the study improved slightly during the follow-up, but none of the untreated eyes with such poor initial visual acuities showed improvement.

**Discussion**

This study confirms previous results that diabetic maculopathy benefits from treatment with xenon arc photoocoagulation. There are, however, some important differences between the results reported here and those reported in 1975. In the previous report, while the initial visual acuity was similar in the treated and untreated eyes, at 1, 2, and 3 years the treated eyes had 1 line less deterioration of vision than the untreated eyes. This difference seemed to be constant, suggesting that photoocoagulation delays but does not prevent deterioration of vision in this condition. The present report, which includes more patients followed up for a longer period of time, leads us to a different conclusion. Instead of the eyes deteriorating in parallel, with the treated eye having significantly better visual acuity than the untreated, we see that there is divergence increasing over the third, fourth, and fifth years. The treated eyes maintain their visual acuities, but those of the untreated group deteriorate.

That the divergence takes time to appear can be explained by several factors. In the absence of treatment macular oedema increases, but slowly, requiring 3 or more years to show its full effect. While the deposition of hard exudate in the fovea may reduce the visual acuity there is a delay period before the exudate is actually deposited in the small central area where it causes most harm to the vision.

The development of reduced capillary perfusion is slow. It may involve the macular arcade with loss of central vision. The process may be altered by photoocoagulation. It has been shown in the normal cat retina that photoocoagulation alters retinal blood flow and its distribution. It would be interesting to measure blood flow in human capillary beds. That would show whether photoocoagulation redistributes flow in such a way that central areas, such as the macula, may have their blood supply enhanced.

Finally, some patients lose vision from complications of new vessel formation. These take several years before visual loss becomes apparent.

The results of treatment are not as marked as for new vessels. A cause of the limited divergence is that irreversible damage to foveal receptors may have occurred even in the treated eye before entry into the trial; once foveal receptors are destroyed by exudate or oedema they cannot regenerate. If these morphological changes were reversible, there would be an earlier more marked divergence in visual acuity, brought about by an improvement in function in treated eyes with resolution of the oedema or exudate.

A further cause of lack of dramatic change in vision is that treatment itself is associated with a degree of morbidity with some visual deterioration which, though it usually improves, does not do so completely.

In the previous paper patients with initial visual
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acuity of 6/6 and 6/9 were reported not to have benefited from treatment. In the small number followed up here, again there was no significant treatment benefit obtained up to 3 years, but after that time the difference in deterioration was over 4 lines of visual acuity in favour of treatment. These results are striking and indicate that early treatment of maculopathy, such as that associated with circinate exudates, may prevent visual loss in these patients at a later stage. The ideal time of treatment is therefore before any marked visual loss has occurred. However, in spite of these results caution in decision of early treatment may be indicated, especially if there is no previous recorded visual deterioration. The number of patients in this group is small. Perhaps we should not therefore be hasty in drawing very firm conclusions from this result, though it was statistically highly significant, especially as treatment does carry a risk of morbidity. Extension of hard exudates in the immediate post-treatment period is common, presumably because of transient increase in leakage. If the hard exudates are near the fovea, they may extend into it, causing profound visual loss.

This study, like the previous one by Patz et al.7 and the earlier report on the same patients7 confirms that poor initial visual acuity precludes good response to photoocoagulation.

The reduction of blindness in the treated eyes is similar to that reported earlier. It must be emphasised, as it was previously, that new vessels and their complications were an important primary and secondary cause of visual loss in these patients. It could be argued that in the treated group this could have been prevented by initial extensive pattern bombing (scatter treatment) of the retinal periphery. However, because in maculopathy there is a loss of central vision, the aim was to preserve peripheral field, and scatter treatment was not given routinely. At the time of starting this study the natural history of new vessels was not clearly established, and this is why patients with early new vessels were included in the maculopathy study. However, the major cause of visual loss in both treated and untreated eyes was progression of the maculopathy. The difference in deterioration therefore cannot be ascribed to the treatment of proliferative retinopathy. The results, however, emphasise the importance of regular follow-up of patients with diabetic maculopathy, including careful examination of the disc and peripheral retina. Careful examination is important, because in this group of elderly patients frequent lens and vitreous opacities make detection of early new vessels difficult. Indeed, they were never diagnosed prior to the vitreous haemorrhage in some of the patients.

During the period of this study we have become aware of the fact that maculopathy is not a single entity but comprises a variety of subgroups which are differentiated by the relationship of hard exudates and haemorrhages, ischaemia, and oedema. These features determine not only the initial visual acuity but also response to treatment. Subdivision into these subgroup depends on analysis of colour photographs and fluorescein angiograms and is in process.

The results reported in this paper were achieved with the xenon arc photoocoagulator. The argon laser will probably be more rather than less effective in the treatment of maculopathy because of its smaller spot size. A randomised study using the laser is now starting in the USA. In the meantime it is suggested, as the result of the findings reported in this paper, that photoocoagulation is an effective way of treating diabetic maculopathy and maintaining vision provided the initial acuity is better than 6/36.

We thank all the research fellows who helped with the study during the follow-up period and without whom we could not have managed the work. In particular we are grateful to Dr Margaret Kearns, who was looking after the largest group of patients almost single-handed for 6 months. We also wish to thank Miss S. Suen, who did all the computing work and drew the graphs. The illustrations were prepared by Mr K. Sehmi and manuscripts typed by Mrs R. Hodgetts and Miss C. Giffen.

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References

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