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Photocoagulation for proliferative diabetic retinopathy: a randomised controlled clinical trial using the xenon-arc

British Multicentre Study Group

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Summary. The final results of a randomised controlled study of xenon-arc photocoagulation for proliferative retinopathy are reported, after all patients have been followed for at least 5 years and some for up to 7 years. One hundred and seven patients with two similarly affected eyes had one treated (chosen by a random procedure), while the other eye remained untreated and served as a control. Of the 107 patients, 77 completed the 5 year follow up, 13 died and 17 stopped attending for various reasons. Of the recorded coexistent medical abnormalities, only renal complications affected survival, none influenced visual outcome. Visual outcome was significantly better in the treated than in the control eyes at each yearly interval ($0.001 < p < 0.05$). The greatest difference was seen in those with disc vessels at entry. In this group, control eyes deteriorated by a mean of four lines on the Snellen chart, treated eyes by one line only. Six patients became legally blind in both eyes, four were blind in the treated eye only, but 28 control eyes were blind when treated eyes retained vision ($p < 0.001$). Treated eyes which became blind had less treatment than those that retained vision. Of the 42 treated eyes with peripheral new vessels only at entry, 12 developed disc new vessels. These 12 had fewer burns than the 30 which did not develop disc new vessels. It is concluded that in proliferative retinopathy, treatment by photocoagulation is better than no treatment at all. Adequate treatment is required to maintain vision.

Key words: Diabetic retinopathy, proliferative retinopathy, xenon-arc photocoagulation, randomised controlled clinical trial.

Since the introduction of photocoagulation for the treatment of diabetic retinopathy by Meyer-Schwickerath [1], three randomised controlled clinical trials have shown its effectiveness in the treatment of proliferative lesions, particularly those which arise from the optic disc [2–5].

The present communication is the final report of one of these studies [3], when all patients have been followed for at least 5 years.

Patients and methods

Patients

Patients with proliferative retinopathy in both eyes were considered for the study. The retinopathy had to be of similar severity in both eyes, i. e. within two grades using the Hammersmith Hospital grading system [6]. This system is based on grading retinal lesions of major importance (microaneurysms and haemorrhages, hard exudates, new vessels and fibrous retinitis proliferans) by comparison with standard photographs. There are four standard photographs for each lesion spanning the full range of severity A–D. This allows six steps of severity grading for each lesion. A lesion can be absent, grade 0; 1 which is better than standard A, 2 which is equal to or worse than standard A, but better than standard B etc, 5 being the worst possible for that lesion. It did not matter whether the new vessels arose from the disc or the retinal periphery. The visual acuity in the two eyes had to be within two lines on the Snellen chart and the vision in the worse eye had to be 6/60 or better. Patients as described above were eligible irrespective of age or duration of diabetes if they fulfilled the following criteria: (1) There was no, or not more than a wisp of, fibrous retinitis proliferans present (< grade 1 of the Hammersmith Hospital grading system [6]). (2) There was no concomitant eye disease which interfered with the photography, assessment or prognosis of the retinopathy. Thus, patients who had had any previous photocoagulation or eye surgery were excluded, as were patients receiving systemic or local therapy for any eye condition. Patients with congenital lesions and amblyopia were also excluded, as were those who had significant assymmetry or refraction (over 2 dioptres). (3) The patient's general health was such that he/she was expected to be followed for 5 years. (4) The patients gave their informed consent for only one eye to be treated and the other to be followed as an untreated control.

There were 107 patients from six participating centres (Hammersmith/Moorfields Hospitals, King's College Hospital and St Thomas' Hospital, London; Kent and Sussex Hospital; Newcastle Eye Infirmary and Bergen Hospital, Norway) who fulfilled the entry criteria and were included in the study. Clinical variables at entry are shown in Tables 1–4.

Table 1. Age of onset and duration of diabetes at entry into study

Known duration of diabetes (years)	Age at diagnosis of diabetes (years)			Total
	0–29	30–59	⩾60	
0– 5	1	19	3	23
6–10	0	6	1	7
11–15	11	4	0	15
16–20	22	3	0	25
Over 20	29	3	0	32
Total	63	35	4	102

Data were missing in five patients

Procedure

After ascertaining the patient's suitability for the trial and obtaining his/her consent for the study, the disc and macular fields of both eyes were photographed. The eye to be treated was determined by a random assignment, prepared at the coordinating centre, and indicated in a sealed envelope, marked with the patient's serial number and opened after the patient's entry into the trial.

Treatment

Treatment was started as soon as possible after randomisation under local (retrobulbar) or general anaesthesia, using the xenon-arc photocoagulator (Zeiss, Oberkochen, FRG or O'Malley, Palo Alto, California, USA). The number of burns given was not specified, but advice was given to treat all peripheral new vessels focally, destroying the vessels as far as possible with a rim of photocoagulation extending approximately one-quarter of the disc diameter beyond the edge of the lesions. Disc new vessels could be treated directly if they came off the disc in the nasal, superior or inferior quadrants. In addition to focal treatment, pattern bombing or scatter treatment could be given to patients with peripheral new vessels in addition to focal treatment, but was not mandatory. Scatter treatment was advised for new vessels arising from the disc, but the number of burns was not specified. Burns were not to be given within 1 disc diameter from the centre of the fovea. The individual burns were of 3° size with a 1-s exposure in the periphery and 1° in the perimacular area, the power varying between setting II and VIII; the aim being to achieve the slightest visible whitening of the retina.

The initial treatment could be given in one or more sessions during the first 3 months. Treated eyes could be retreated at any time if further new vessels developed or the vessels present initially became worse. The control eye remained untreated until after 1977, when the British Multicentre Study report became available and significant benefit from treatment in disc new vessels was observed [3]. Thereafter, the control eye could be treated if it had disc new vessels worse than Hammersmith Hospital grade 1 [7]. There were only two such eyes and these patients were excluded from further analysis. A further 28 were considered already untreatable.

Yearly eye examination, photographic grading and relevant medical details were obtained as near as possible to the anniversary of entry into the study and a computer used for their analysis.

Eye examination included the best corrected visual acuity obtained on the Snellen chart (taken when possible by an optician unaware of which eye was treated). The Snellen chart was a standard back-illuminated model and no further effort of standardisation between clinics was performed. However, in each centre, the same chart was used throughout the study and the treated and control eyes were treated similarly. Full clinical examination of the eye was performed, including slit lamp biomicroscopy and indirect and direct ophthalmoscopy. Photographs (non-stereoscopic) of the disc and macular fields were taken. Fluorescein angiography did not form part of the study. For photographic grading, the Hammersmith Hospital grading system was used [6, 7].

Statistical methods

For statistical analysis, the paired t-test, McNemar's test [8] and Chi-square test were used. A paired t-test was used to compare treated and control eyes for mean visual acuity and the change of vision at each yearly interval for treated and control eyes. To allow statistical analysis, the visual acuity was converted to a numerical grade: 6/6=1, 6/9=2, etc., as described previously [3]. It was also used to compare the photographic grading between the treated and control eyes. McNemar's test was used to compare the numbers of eyes that improved, remained the same, or deteriorated. For this analysis, improvement or deterioration were defined as a change of two lines or more in visual acuity on the Snellen chart. McNemar's test was also used to compare blind and seeing eyes. Blindness was defined as a visual acuity of 6/60 or worse at two successive yearly assessments. This visual acuity was chosen, as 6/60 vision in the better eye allows legal blind registration in the UK. The Chi-square test was used to compare the clinical characteristics of patients dying or surviving and those retaining vision or becoming blind. It was also used to compare the number of assessable eyes at each yearly interval.

For the visual acuity analysis, patients were first considered as a group. They were then subdivided into those with new vessels on the disc in both eyes and peripheral vessels only in both eyes and those asymmetrical for origin of new vessels. Because of the small number of asymmetrical eyes, these were not analysed separately.

Results

There were 107 patients from the six centres who entered the study. Of these, 77 completed five years of follow-up. Of the remainder, 13 were known to have died (four from renal failure, four from coronary heart disease, three following a stroke, one of cancer and one of unknown cause). Another 17 failed to complete the five-year follow up, two because they had the control eye treated, three were too ill to come to hospital, four were blind and the journey was too long, five had moved house and three because the ophthalmologist had moved hospitals.

Medical conditions of the patients studied

Age at diagnosis and duration of diabetes in 102 of the 107 patients are shown in Table 1 and their clinical details in Table 2. Sixty-three patients were diagnosed as diabetic before the age of 30 years and they were all insulin-dependent. Two-thirds of the patients had had their disease for >15 years. With increasing age of onset, the duration of diabetes before proliferative retinopathy developed became shorter. There were more male than female patients. At least 20 patients were non-insulin-dependent.

Of the coexistent medical conditions, neuropathy was the commonest, raised blood pressure was next, followed by raised blood urea (Table 3). However, none of the 39 with elevated urea had levels >11.5 mmol/l. Proteinuria was also common, but cardiac changes and claudication were uncommon. None of these condi-

Table 2. Details of patients with new vessels

Sex M/F	Age at diagnosis of diabetes (years)	Age at entry to study (years)	Duration of diabetes at entry to study (years)	Treatment		
				Number on diet ± oral hypoglycaemic agent	Number on insulin	Number not known
64/43	26.5 ± 1.8 (1–65)	42.4 ± 1.3 (19–70)	16.4 ± 1.1 (0–51)	20	83	4

Results expressed as mean ± SEM with range in parentheses

Table 3. Medical condition at entry into the study in 107 diabetic patients

	Elevated systolic blood pressure	Elevated diastolic blood pressure	Elevated blood urea	Proteinuria	Peripheral neuropathy	ECG change or angina	Intermittent claudication
Present	39	28	39	18	67	4	3
Absent	65	76	57	85	38	101	102
Unknown	3	3	11	4	2	2	2

Upper limits of normal: systolic blood pressure: 159 mmHg; diastolic blood pressure: 89 mmHg; blood urea: 6.5 mmol/l

Table 4. Difference in deterioration between treated and control eyes

	Year of follow-up	No. of Patients	Mean difference in deterioration between treated and untreated eyes[a]	p
All patients	1	107	0.52 ± 0.26	< 0.05
	2	99	0.96 ± 0.28	< 0.001
	3	99	1.79 ± 0.33	< 0.001
	4	88	1.73 ± 0.37	< 0.001
	5	76	1.96 ± 0.44	< 0.001
	6	37	1.89 ± 0.57	< 0.01
	7	15	2.67 ± 1.11	< 0.05
Patients with disc new vessels at entry	1	55	1.04 ± 0.42	< 0.02
	2	52	1.64 ± 0.38	< 0.001
	3	52	2.78 ± 0.45	< 0.001
	4	46	2.61 ± 0.52	< 0.001
	5	39	2.97 ± 0.63	< 0.001
	6	19	2.47 ± 0.85	< 0.01
	7	9	3.33 ± 1.57	NS
Patients with only peripheral new vessels at entry	1	42	0.07 ± 0.31	NS
	2	38	0.45 ± 0.44	NS
	3	38	0.87 ± 0.49	NS
	4	34	0.34 ± 0.53	NS
	5	30	1.10 ± 0.61	NS
	6	17	1.29 ± 0.79	NS
	7	6	1.67 ± 1.52	NS

Results expressed as mean ± SEM. [a] $(VA_{u1}-VA_{u0}) - (VA_{t1}-VA_{t0})$ where VA = visual acuity, u and t untreated and treated eyes at initial (0) and 1 year (1)

tions influenced visual outcome. Those with persistent or intermittent proteinuria had significantly higher mortality than those without proteinuria ($p < 0.05$). None of the other medical conditions significantly influenced survival.

Visual outcome

Visual acuity changes. While the treated and control eyes had similar vision at the beginning of the study, after one year the deterioration was significantly greater in the control than in the treated eyes, the difference being half a line in visual acuity ($p < 0.05$, Fig. 1 and Table 4). This increased to a maximum of 2½ lines in the 15 patients followed for 7 years ($p < 0.05$), but had almost reached two lines at 4 and 5 years ($p < 0.001$).

When patients with new vessels arising from the optic disc were considered separately from those who had only peripheral new vessels, there was a highly significant difference in favour of treatment in the former group at each yearly interval, reaching almost three lines at 5 years ($p < 0.001$, Fig. 2, Table 4). In contrast, patients with peripheral vessels only showed no significant difference at any time, although even in that group the untreated eyes deteriorated more than the treated eyes (Fig. 2, Table 4).

Table 5 compares those eyes that improved by two lines or more, or remained within two lines of their original vision, or deteriorated by two lines or more in the treated and control groups. This indicates that between the second and sixth year, fewer treated than control eyes deteriorated, while more treated eyes retained their vision or improved ($0.05 < p < 0.001$).

Figure 3 illustrates the visual outcome of individual eyes with proliferative retinopathy at 5 years. In the treated group, only seven eyes with initial visual acuity of 6/6–6/12 deteriorated by more than two lines and only eight eyes reached the level of blindness (6/60 or worse vision), one of which was already blind at entry. In contrast, among the control eyes with similar initial vision, 28 deteriorated by more than two lines and 27 out of 77 reached the level of blindness.

The difference was even more marked when patients with only disc new vessels were considered, where not a single control eye improved and only nine stayed within one line of their original vision. In twenty-one, vision, deteriorated to 6/60 or worse. Twenty-five treated eyes improved or remained within one line of their initial vision and only six became blind, one being blind at entry (Fig. 4).

Blindness. Six patients became blind in both their treated and control eyes, four only in the treated eye when the control eye could still see and 28 in the control eye only, when the treated eye retained vision ($p < 0.001$). The difference was only significant when patients with disc new vessels were considered, although even in the peripheral new vessel group, more control eyes (five) than treated (one eye) became blind (Table 6). The causes of blindness were complications of new vessels in every case; vitreous haemorrhage, fibrous retinitis proliferans, retinal detachment and thrombotic glaucoma, either alone or in combination.

Treatment effects

Twenty-eight eyes had focal treatment only, 39 had scatter treatment alone, while 40 had both focal and scatter treatment. Forty-eight patients had all their treatment during the first month, 59 had one or more treatment sessions during subsequent years. As the number of burns to be given was not specified, in general, treatment given in the first 2 years was less than in later years, when experience with the instrument and reaction to treatment influenced the operator. The nine treated eyes with new vessels on the disc (one assymetrical eye, which went blind, had disc vessels in the treated eye) which became blind had fewer burns (mean 187) than the other 46 who retained vision (mean 316) (Table 7). Because of the size of the xenon-arc burns, 316 applications (probably even 150–200) invariably meant scatter treatment (though the initial treatment may have been focal). There were 12 patients who started with peripheral new vessels only and developed new vessels on the disc in their treated eye. These 12 had fewer burns (mean 117) before the development of the new vessels, compared with those who did not develop disc vessels (mean 189). Following the development of disc vessels, they had a further mean application of 211 burns (range 33–941). They also had more scatter treatment and less focal treatment.

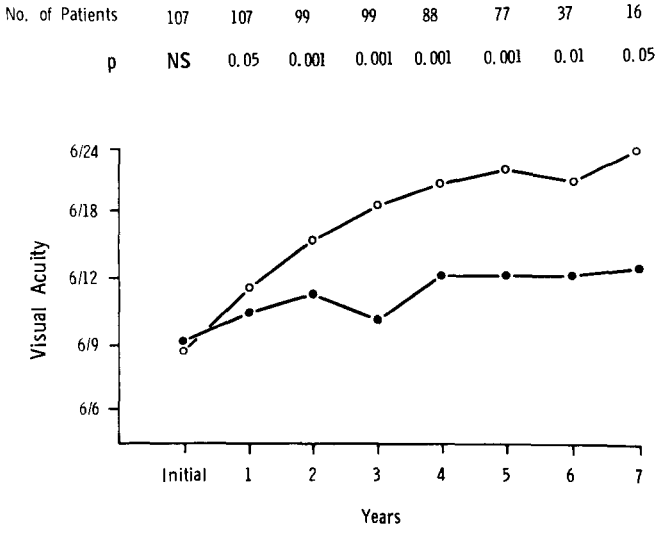

Fig. 1. Mean visual acuity of all eyes with new vessels. O——O control eyes, ●——● treated eyes

Photographic grading

At the initial examination, there was no significant difference between treated and control eyes. Thereafter, at each yearly interval, there was a significant difference in at least some of the retinopathy features. Haemorrhages and microaneurysms were significantly less in the treated than control eyes from 1 to 5 years ($0.02 < p < 0.001$), while hard exudates were less in the macular field only after the third year. It is of importance that the disc new vessel grading was highly significantly lower in treated than control eyes, reaching 0 grading (absent) by 7 years (Fig. 5). This was not because the new vessels changed

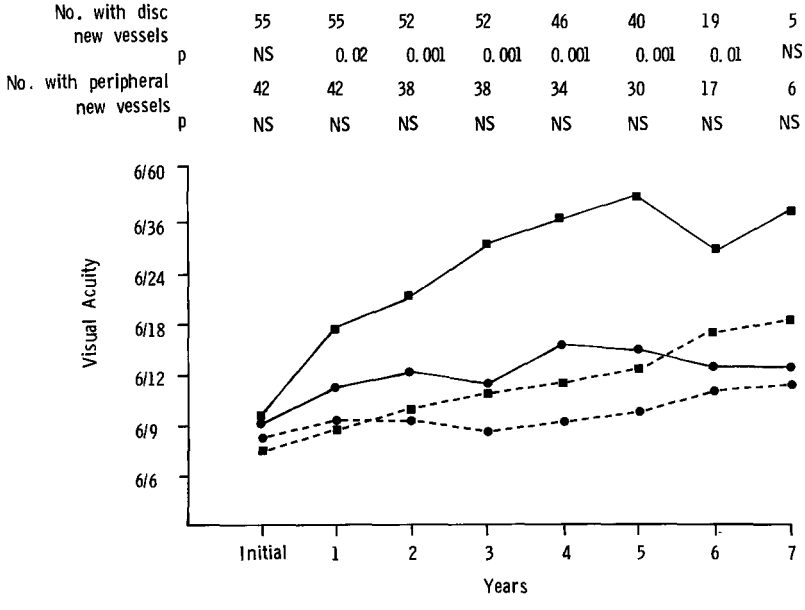

Fig. 2. Mean visual acuity of control eyes with disc new vessels ■——■, treated eyes with disc new vessels ●——●, control eyes with peripheral new vessels only ■- - -■, treated eyes with peripheral new vessels only ●--●

Table 5. McNemar's test comparing eyes that improved and deteriorated in the treated and control groups

			Control eye		Total	p
			Improved/same	Worse		
After 1 year	Treated eye	Improved/same	71	19	90	
		worse	12	5	17	
		Total	83	24	107	NS
After 2 years	Treated eye	Improved/same	57	20	77	
		worse	8	14	22	
		Total	65	34	99	<0.05
After 3 years	Treated eye	Improved/same	47	34	81	
		worse	6	12	18	
		Total	53	46	99	<0.001
After 4 years	Treated eye	Improved/same	35	30	65	
		worse	10	13	23	
		Total	45	43	88	<0.01
After 5 years	Treated eye	Improved/same	29	28	57	
		worse	6	13	19	
		Total	35	41	76	<0.001
After 6 years	Treated eye	Improved/same	14	12	26	
		worse	3	8	11	
		Total	17	20	37	<0.05

McNemar's test: Chi-square $= \frac{[(b-c)-1]^2}{b+c}$ where b = number worse in control eye and improved or same in treated eye and c = number improved or the same in the control eye and worse in the treated eye. p refers to the test for difference between treated and control eyes. Improved = improved by two lines or more on Snellen chart; worse = deteriorated by two lines or more on Snellen chart; NS = not significant.

to fibrous retinitis proliferans, but rather because they improved, since in the treated eyes, less fibrous tissue formed (Fig. 6). Indeed, the mean grading for fibrous tissue remained unchanged in the treated eyes while it deteriorated in the control eyes, so that it became significantly worse at 3, 4, 5 and 7 years ($0.05 < p < 0.001$). More control eyes became unassessable than treated ones; vitreous haemorrhage, thrombotic glaucoma and detachment being the principle causes. The difference in assessability was significant at 3, 4 and 5 years ($p < 0.05$).

Discussion

The aim of this study was to establish the value of xenon-arc photocoagulation in the treatment of diabetic retinopathy. In allowing a certain amount of freedom in the treatment technique, it was also aimed at finding the best possible treatment method. In both these aims, the trial was successful.

The report re-emphasizes the result of three short-term [2–4] and one long-term randomised controlled clinical studies [5] in the treatment of proliferative diabetic retinopathy. Of the previous studies, those of the "Diabetic Retinopathy Study Group" are the most important, because of the highly significant results obtained in a study of more than 1700 patients [2, 5]. It is noteworthy that the cumulative rate of severe visual loss (similar to blindness in our study) in the control eyes of that study was 34% at 5 years, similar to that of the present study (34 out of 107 eyes). The 15% blindness in their treated eyes is also similar to that found in the United Kingdom. The results are slightly worse than those found by Asher et al [9], who analysed one group's result over a long period of time, though this was not a randomised controlled clinical study. Part of the reason for Asher et al's better results may be that the correct

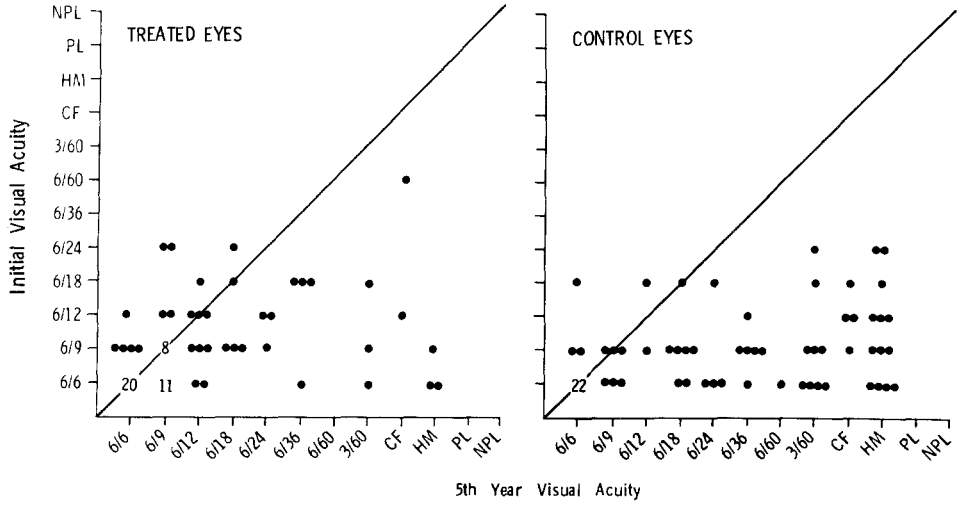

Fig. 3. Initial and 5-year visual acuity in 77 treated and control eyes with proliferative retinopathy at entry into the study. Each eye is represented by a dot (or by number if over six in one spot). Diagonal: no change line, CF = count fingers, HM = hand movements, PL = perception of light, NPL = no perception of light

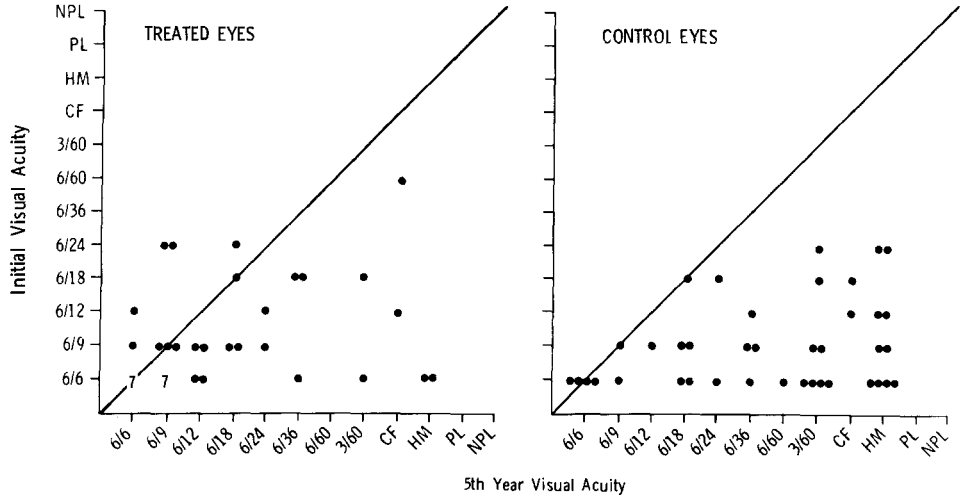

Fig. 4. Initial and 5-year visual acuity of 40 treated and 39 eyes with disc new vessels at entry into the study Annotation as in Figure 3

Table 6. Blindness in eyes with new vessels

New vessels	No. of blind eyes			*p*
	Both eyes	Treated eyes only	Control eyes only	
On disc	6	2	22	<0.001
Peripheral only	0	1	5	NS
Asymmetrical	0	1	1	NS
Total	6	4	28	<0.001

NS = not significant

Table 7a. Effect of treatment on eyes with disc new vessels

	No. of eyes	No. of burns mean (range)
Blind	9	187 (68–336)
Not blind	46	316 (25–860)
Total	55	

Table 7b. Development of disc new vessels (absent at entry)

	Treated eyes	No. of burns mean (range)	Control eyes
Disc vessels developed	12	117 (12–276)	21
Disc vessels did not develop	30	189 (33–580)	21
Total	42		42

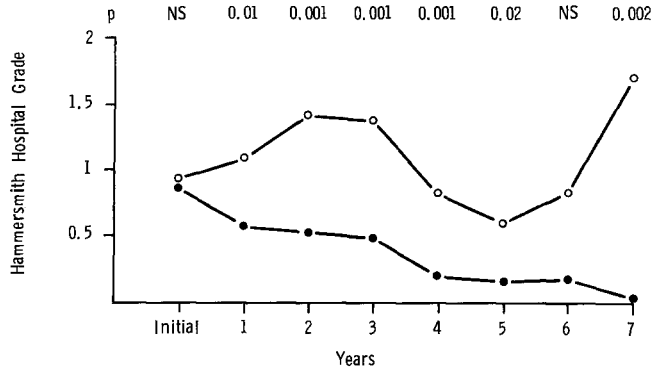

Fig. 5. Mean new vessel grading in the disc field in treated (●——●) and control (○——○) eyes. NS: not significant

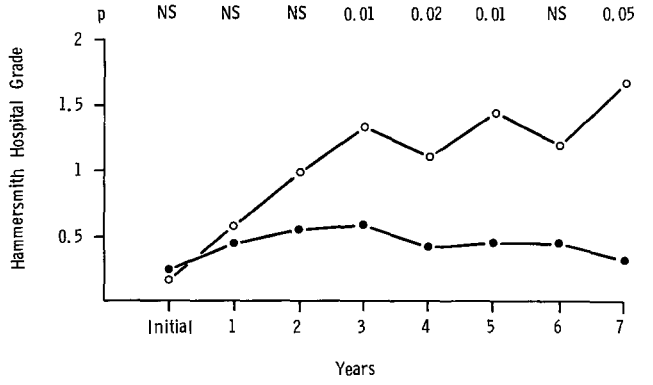

Fig. 6. Mean grading of fibrous retinitis proliferens in the disc field for treated (●——●) and control (○——○) eyes. NS: not significant.

treatment is most likely to be utilised reliably in a small group working together and devoted to the management of diabetic eye disease.

In this study, only xenon treatment was used while Hercules et al used argon only [4]. The Diabetic Retinopathy Study Group used both xenon and argon [2, 5, 10]. The results with xenon were slightly, but not significantly, better in preventing blindness, but more xenon than argon-treated eyes lost a few lines of vision as a result of treatment [2]. The reason may have been the protocol designed by the Diabetic Retinopathy Study Group which specified that focal treatment should be given to lesions if they were responsible for macular oedema [10]. Such lesions would commonly be within one disc diameter of the fovea – an area avoided in the present study.

The second aim of the present study was to find a method of treatment which would be acceptable to all in clinical practice. The freedom allowed in the study prevented a randomised comparison of methods, but the results provide a strong indication for extensive treatment rather than a scattered one and for scatter plus focal treatment for peripheral new vessels. The study also showed (probably because xenon only was used) that direct treatment of vessels on the disc or feeder vessel treatment is rarely indicated. Indeed the method of treatment advised by the Diabetic Retinopathy Study Group study [10] is not now used, as clinical practice clearly showed that more extensive treatment and not direct treatment of disc vessels is more advantageous [3]. The idea of scatter treatment alone as a useful method of management of proliferative diabetic retinopathy originates from Aiello et al. [11].

The present study, like those previously published, emphasises the effectiveness of photocoagulation in patients with new vessels arising from the optic disc. When untreated, these have a poor prognosis, even in those with early lesions [12]. Caird et al. [13] reported that within 3 years of their first vitreous haemorrhage, one-third of patients were blind in *both* eyes. Vitreous haemorrhage is an early complication of disc new vessels, but occurs relatively late only in those with peripheral new vessels. The latter only bleed when they grow forward off the surface of the retina. Nevertheless, flat new vessels should probably be treated, because it is easy to do so, and because as shown here, within 5 years, 50% develop disc new vessels when untreated. Twenty-eight percent of the treated eyes also developed disc new vessels; they tended to be the eyes which had received less treatment, and further treatment destroyed these vessels or caused regression.

It is not surprising that in this study, medical conditions did not influence visual outcome. New vessels arise in response to a non-perfused retina; they are not the direct result of high blood pressure or poor metabolic control. It is likely that, early in diabetes, these factors are important, as they may lead to more rapid and widespread vascular occlusion, but this has not yet been proven.

It is of interest that only 14% of the patients died during the follow-up period. The 5-year mortality in the study by Davis et al. [14] in those with proliferative retinopathy was 50%. However, the patients in that study were selected on ophthalmic criteria only, while here only those likely to survive 5 years were entered.

Finally, the large majority of patients in this study had 6/12 or better vision at entry into the study and were not aware of any visual impairment. Yet one-third of all untreated eyes were blind with a visual acuity of 6/60 or worse for two consecutive yearly assessments after 5 years of follow-up. This emphasises the need for screening of patients, especially those with young onset insulin-dependent diabetes, for proliferative retinopathy. Early lesions are easy to treat and, with adequate treatment, visual prognosis is predictably good.

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References

1. Meyer-Schwickerath G (1979) Lichtkoagulation. Enke Verlag, Stuttgart
2. Diabetic Retinopathy Study Research Group (1976) Preliminary report on effects of photocoagulation therapy. Am J Ophthalmol 81: 383–397
3. British Multicentre Study Group (1977) Proliferative diabetic retinopathy; treatment with xenon arc photocoagulation. Br Med J 1: 739–742
4. Hercules BL, Gayed II, Lucas SB, Jaecock J (1977) Peripheral retinal ablation in the treatment of proliferative diabetic retinopathy. Br J Ophthalmol 61: 555–563
5. Diabetic Retinopathy Study Research Group (1981) Photocoagulation treatment of proliferative diabetic retinopathy. Diabetic Retinopathy Study, report No. 8. Ophthalmology 88: 583–600
6. Oakley NW, Hill DW, Joplin GF, Kohner EM, Fraser TR (1967) Diabetic retinopathy I: assessment of severity and progression with a set of standard fundus photographs. Diabetologia 3: 402–405
7. Kohner EM, Panissett A, Cheng H, Fraser TR (1971) Diabetic retinopathy. New vessels arising from the optic disc I: grading system and natural history. Diabetes 20: 816–823
8. Armitage P (1971) Statistical methods in medical research. Blackwell, Oxford, p 128
9. Asher R, Hunt S, Hamilton AM, Townsend C, Blach RK, Khoury D, Kohner EM, Morris DV (1981) Photocoagulation for optic disc new vessels in diabetic retinopathy. Int Ophthal 3: 79–85
10. Diabetic Retinopathy Study Research Group (1981) Design methods and baseline results. Invest Ophthalmol Vis Sci 21: 149–203
11. Aiello LM, Beetham WP, Baodimos MC, Chazan BI, Bradley RF (1969) Ruby laser photocoagulation in the treatment of proliferative diabetic retinopathy. In: Goldberg M, Fine S (eds) Treatment of diabetic retinopathy. United States Department of Public Health, pp 437–463
12. Deckert T, Simonson E, Poulsen JE (1967) Prognosis of proliferative retinopathy in juvenile diabetes. Diabetes 16: 728–737
13. Caird FI, Burditt AF, Draper GJ (1968) Diabetic retinopathy. A further study of prognosis for vision. Diabetes 17: 121–123
14. Davis MD, Hiller R, Magli YL, Podgor MJ, Ederer F, Harris WA, Long JW, Haug GA (1979) Prognosis for life in patients with diabetes in relation to severity of retinopathy. Trans Amer Ophth Soc 77: 144–170

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