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Type 1 diabetes patients with severe non-proliferative retinopathy may benefit from panretinal photocoagulation

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ABSTRACT.

Purpose: To examine whether panretinal photocoagulation for severe non-proliferative retinopathy in type 1 diabetes patients could halt the progression of retinopathy with subsequent vitreous haemorrhages and visual impairment.

Methods: During a 10-year follow-up study period of 344 type 1 diabetes patients, 81 subjects went through panretinal photocoagulation. Forty patients were treated for severe non-proliferative retinopathy (age at onset of diabetes 14 ± 8 years, diabetes duration 18 ± 10 years) and 41 for proliferative retinopathy (age at onset 15 ± 10 years, diabetes duration 22 ± 13 years). One randomly selected eye per patient forms the basis for the study. Metabolic control, systolic and diastolic blood pressure, serum creatinine and urinary albumin levels were measured and analysed yearly during the follow-up period.

Results: A total of 35% (14/40) of eyes treated for severe non-proliferative retinopathy developed neovascularizations during a mean time of 2.9 ± 1.5 years. Vitreous haemorrhages were more frequent in eyes with proliferative retinopathy at treatment than in eyes with severe non-proliferative retinopathy (12/41 versus 2/40; $p = 0.007$). The number of vitrectomies due to vitreous haemorrhages in eyes treated for severe non-proliferative retinopathy tended to be lower (1/40 versus 6/41; $p = 0.052$). Before photocoagulation, visual acuity (VA) was similar in eyes with severe non-proliferative retinopathy and in those with proliferative retinopathy (1.0, 0.4–1.0 versus 1.0, 0.1–1.0; median and range). Visual impairment and blindness tended to develop more often in eyes treated for proliferative retinopathy compared to those treated for severe non-proliferative retinopathy (10/40 versus 4/40; $p = 0.056$). Eyes with neovascularizations at follow-up were more often visually impaired ($VA < 0.5$) than eyes without neovascularizations (15/55 versus 1/26; $p = 0.016$).

Conclusion: In type 1 diabetes, panretinal photocoagulation may be beneficial even at the severe non-proliferative retinopathy stage in terms of preventing vitreous haemorrhage, subsequent vitrectomy and visual impairment.

Key words: type 1 diabetes – severe non-proliferative/ proliferative retinopathy – panretinal photocoagulation – vitreous haemorrhage – vitrectomy

Introduction

Diabetic retinopathy is still a major cause of visual impairment in middle-aged people in the Western world (Trautner et al. 1997), despite screening (Porta et al. 1995) and widely accepted guidelines for laser treatment (Diabetic Retinopathy Study Research Group 1981; Early Treatment Diabetic Retinopathy Study Research Group 1985). An analysis of the results from the Early Treatment Diabetic Retinopathy Study (ETDRS) group revealed that panretinal photocoagulation for severe non-proliferative or early proliferative retinopathy reduced the rate of visual impairment in patients with type 2 diabetes, whereas this could not be demonstrated in patients with type 1 diabetes (Ferris 1996).

In recent years, a Scandinavian study by Rossing et al. (1998) reported improved visual outcome in type 1 diabetes patients, despite an unchanged incidence of proliferative retinopathy, a finding which could be attributed to more frequent laser treatment. In a previous study of type 1 diabetes patients, we demonstrated that the 10-year incidence of moderate visual impairment was low (8%) and that only two eyes became legally blind (Lövestam-Adrian et al. 2001). The present study of laser treatment approaches aimed to establish whether panretinal photocoagulation in type 1 diabetes patients instituted at

the severe non-proliferative stage might have a more favourable outcome on vitreous haemorrhages, vitrectomies and visual acuity (VA) in comparison with corresponding laser treatment instituted at the proliferative retinopathy stage.

Patients and Methods

Patients

A total of 81 consecutive type 1 diabetes patients treated with panretinal photocoagulation for severe non-proliferative ($n = 40$) or proliferative ($n = 41$) retinopathy, formed the basis for the present study. They represented a subgroup of 452 type 1 diabetes patients examined at the Department of Ophthalmology (Lund) in 1986, out of whom 388 continued to participate in regular eye examinations during the entire 10-year follow-up period ($n = 344$) or until death ($n = 44$) (Lövestam-Adrian et al. 2001). Although the time-point for panretinal photocoagulation was not randomly assigned, the numbers of patients in the severe non-proliferative and proliferative groups ended up almost equal.

One eye per patient was randomly assigned for this study using a computer-based statistical program (SPSS).

Classification of retinopathy

Before laser treatment, the classification of retinopathy was based on findings from fundus photographs using a 45° Topcon camera. Three fields per eye were obtained through dilated pupils, nasal, central with stereo pairs, and temporal fields. The retinopathy was characterized as:

- (1) severe non-proliferative retinopathy, with multiple haemorrhages in four quadrants, venous beading in two quadrants, or intraretinal microvascular abnormalities (IRMA) in one or more quadrants, or
- (2) proliferative retinopathy, with formation of new vessels and/or vitreous haemorrhages.

In addition, the presence or absence of clinically significant macular oedema according to the definition by ETDRS Research Group (1985) was diagnosed according to stereo photographs of the macula.

During follow-up, new vessels as well as the number of vitreous haemorrhages were registered.

Photocoagulation

All eyes were treated with panretinal photocoagulation, 300–500 μ , 0.1–0.2 seconds, at least 1500 burns/eye, in two to four sessions. The number of laser burns given per eye did not differ between those with severe non-proliferative retinopathy and those with proliferative retinopathy. Eyes with diffuse macular oedema or leakage from central microaneurysms were treated with appropriate focal/grid macular photocoagulation prior to panretinal photocoagulation as described by ETDRS Research Group (1985).

Vitrectomy was performed within 3 months in the presence of persistent severe vitreous haemorrhage that obscured visual function.

Visual acuity

Visual acuity (VA) was tested using Snellen Charts. Three levels of VA were defined: normal or moderately affected VA ($VA \geq 0.5$), visual impairment ($VA = 0.4–0.2$), and legal blindness ($VA \leq 0.1$).

Medical risk indicators

Age, age at onset of diabetes, diabetes duration, HbA_{1c}, systolic and diastolic blood pressure, serum-creatinine and urinary albumin were registered before photocoagulation and throughout the follow-up period. For each calendar year, a mean value was calculated and from these an overall mean value was obtained.

Analytical techniques

HbA_{1c} levels were analysed by ion-exchange chromatography using commercially available microcolumns (Bio-Rad, Richmond, California, USA) or by fast liquid chromatography (Kontron Instruments, Milan, Italy). The normal value for both methods is $< 5.3\%$. Blood pressure was measured in the supine position using a mercury sphygmomanometer. Diastolic blood pressure was taken at Korotkoff phase V. Urine was collected in polystyrene tubes and stored at 4° for less than 4 days before analysis. Urinary albumin concentration was measured with an electroimmunoassay using human albumin (Kabi Vitrum, Stockholm, Sweden) (detection limit 12.5 mg/l) or by turbidimetry with an automated analyser (Cobras Mira, Roche, UK), antibodies (rabbit antihuman albumin) and

technique as described by Dakopatts, Copenhagen (detection limit 5 mg/l). Serum creatinine levels were analysed by a kinetic Jaffe reaction or by an enzymatic method (creatinine-hydrolase; EKTA Chem-analyser, Instrument Kodak, New York, NY, USA). The latter method was adjusted to give the same values as the first. Normal values were 48–100 μ mol/l for women and 55–116 μ mol/l for men.

Statistics

Values are given as mean \pm SD or median and range. Student's two-tailed *t*-test was used for equal standard deviations and Welch's approximate *t*-test for unequal standard deviations. Mann-Whitney *U*-test was used for distribution free data and chi-squared test was used for testing categorical variables. Logistic regression analysis with forward stepwise selection was used to establish the independent influence of various risk indicators. All tests were two-tailed and a *p*-value of ≤ 0.05 was considered significant. The statistical analyses were performed using SPSS FOR WINDOWS VERSION 10.

Results

Photocoagulation and progression of retinopathy

The mean times between initiation of treatment and follow-up were similar for both treatment groups (4.0 ± 2.6 years for the severe non-proliferative group versus 4.1 ± 2.5 years for the proliferative retinopathy group).

A total of 35% (14/40) of eyes treated for severe non-proliferative retinopathy developed neovascularizations during a mean period of 2.9 ± 1.5 years. The majority (8/14) of these included high risk characteristics as defined by the Diabetic Retinopathy Study (DRS) (Diabetic Retinopathy Study Research Group 1981). Vitreous haemorrhages occurred more frequently in eyes treated for proliferative retinopathy than in those treated for severe non-proliferative retinopathy (12/41 versus 2/40; $p = 0.007$) (Fig. 1). The mean time from initiation of laser treatment to occurrence of vitreous haemorrhages was 3.1 ± 2.7 years.

There was a trend towards a lower number of vitrectomies due to vitreous haemorrhage in eyes treated for severe non-proliferative retinopathy than in eyes with proliferative retinopathy at

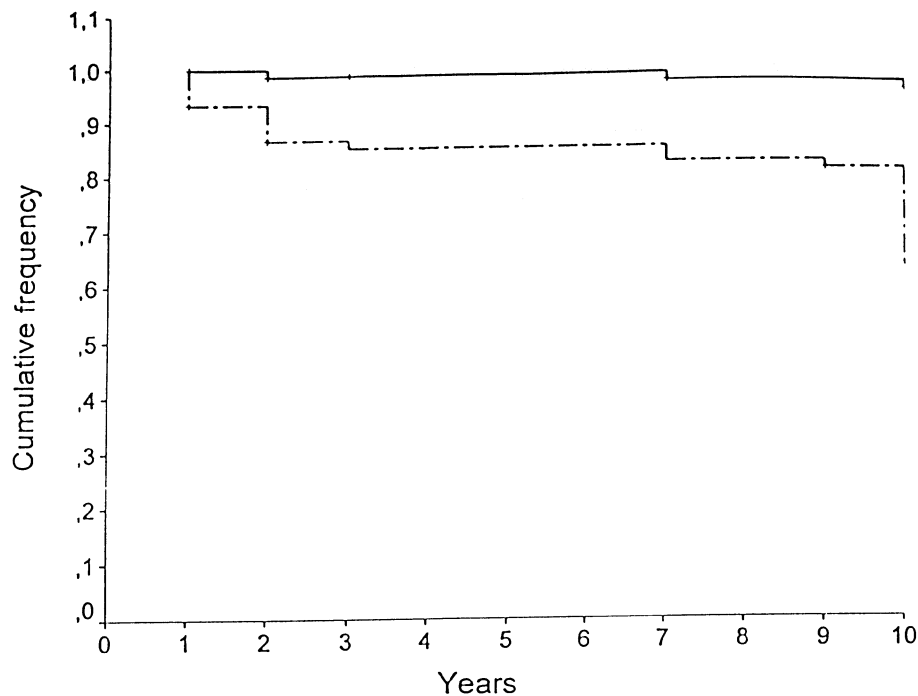


Fig. 1. The 10-year cumulative frequency of patients without vitreous haemorrhage throughout the study. Full line: eyes treated for severe non-proliferative retinopathy. Dotted line: eyes treated for proliferative retinopathy.

the time of photocoagulation (1/40 versus 6/41; $p = 0.052$).

In all, 80% (32/40) of eyes treated for severe non-proliferative and 68% (28/41) of eyes treated for proliferative retinopathy (NS) had diffuse oedemas or leaking microaneurysms in the centre of the macula and received focal/grid laser photocoagulation prior to pan-retinal treatment.

No eye developed retinal detachment or neovascular glaucoma.

Visual acuity

Visual acuities prior to laser treatment and at follow-up are shown in Table 1. Before photocoagulation, VA was

similar in eyes treated for severe non-proliferative retinopathy and for proliferative retinopathy (median 1.0, range 0.4–1.0 versus median 1.0, range 0.1–1.0). Visual impairment and blindness tended to develop more often in eyes treated for proliferative retinopathy compared to those treated for severe non-proliferative retinopathy but the difference was of borderline significance (10/38 versus 4/40; $p = 0.056$). Visual impairment developed in 1/27 eyes treated for severe non-proliferative retinopathy without progression to proliferative retinopathy. The corresponding figure for those eyes which showed progression to proliferative retinopathy was 3/13. None became legally blind.

Eyes with neovascularizations at follow-up were more often visually impaired ($VA < 0.5$) than eyes without neovascularizations (15/55 versus 1/26; $p = 0.016$).

At follow-up, the numbers of visually impaired eyes were similar in those treated for diffuse macular oedema or leaking microaneurysms prior to pan-retinal photocoagulation to those which had not been so treated before pan-retinal coagulation (12/62 versus 3/19). None of the eyes developed fibrous tissue in the vitreous or neovascular glaucoma.

Medical risk indicators

The medical risk indicators for development of retinopathy are shown in Table 2. There were no differences in any of the parameters between patients treated for severe non-proliferative retinopathy and patients treated for proliferative retinopathy either before or throughout the observation period.

Table 1. Visual acuity and degree of retinopathy prior to photocoagulation and at follow-up.

| Visual acuity and degree of retinopathy prior to photocoagulation | Visual acuity and degree of retinopathy at follow-up | | | | | |
|---|--|---------|------------|---------------------------|---------|------------|
| | ≥ 0.5 | 0.4–0.2 | ≤ 0.1 | ≥ 0.5 | 0.4–0.2 | ≤ 0.1 |
| Severe non-proliferative retinopathy | Severe non-proliferative retinopathy | | | Proliferative retinopathy | | |
| ≥ 0.5 (n = 40) | 26 | 1 | | 10 | 3 | |
| 0.4–0.2 (n = 0) | | | | | | |
| ≤ 0.1 (n = 0) | | | | | | |
| Proliferative retinopathy | | | | | | |
| ≥ 0.5 (n = 36) | | | | 28 | 8 | |
| 0.4–0.2 (n = 4) | | | | 1 | 1 | 2 |
| ≤ 0.1 (n = 1) | | | | | | 1 |

Discussion

The risk of development of high risk proliferative retinopathy in non-photocoagulated eyes with severe non-proliferative retinopathy is high (DRS Research Group 1978; ETDRS Research Group 1991a, 1991b). The

Table 2. Comparison of patient characteristics between those with severe non-proliferative and those with proliferative retinopathy.

| | Severe non-proliferative retinopathy (<i>n</i> = 40) | Proliferative retinopathy (<i>n</i> = 41) |
|--|---|--|
| Age at onset (years) | 14.4 ± 7.8 | 15.0 ± 9.2 |
| Diabetes duration (years) | 18 ± 10 | 22 ± 13 |
| HbA _{1c} (%) | 9.1 ± 1.0 | 9.0 ± 1.2 |
| SBP (mmHg) | 135 ± 12 | 141 ± 19 |
| DBP (mmHg) | 79 ± 6 | 80 ± 6 |
| Urinary albumin (mg l ⁻¹) | 72 (0–9350) | 86 (0–5375) |
| Serum creatinine (μmol l ⁻¹) | 69 (51–651) | 74 (51–748) |
| Insulin dose (U kg ⁻¹) | 0.66 ± 0.16 | 0.64 ± 0.21 |

Values are given as mean ± SD and as median and range. The values given are the mean values for all measurements during the observation period.

SBP = systolic blood pressure; DBP = diastolic blood pressure.

ETDRS reported a 44% risk within 3 years (ETDRS Research Group 1991a). In the present study, despite panretinal photocoagulation for severe non-proliferative retinopathy, 35% of eyes developed new vessels within 3 years and 57% of those showed signs of high risk proliferative retinopathy. This is comparable to the ETDRS study, in which 20% of treated eyes developed high risk proliferative retinopathy (ETDRS Research Group 1991a) and demonstrates the progressive nature of severe non-proliferative retinopathy and risk of visual impairment due to vitreous haemorrhage.

The occurrence of vitreous haemorrhage (29%) in eyes with proliferative retinopathy at the time of treatment was similar to the frequency reported by Vander et al. (1991). Most of the vitreous haemorrhages occurred within the first 3 years after photocoagulation and thereafter the frequency declined. Vitreous haemorrhage is the most frequent cause of visual loss (ETDRS Research Group 1999) and as we were able to demonstrate that, despite the development of neovascularizations, vitreous haemorrhages could be avoided in most cases treated for severe non-proliferative retinopathy, our study indicates that early panretinal photocoagulation may be beneficial at this early stage.

The frequency of visually impaired eyes was 14% (11/81), representing a range similar to that found by the (1991a) ETDRS No 9, where 12% of eyes were found to be visually impaired (< 20/40). We have not used the same criteria for more severely affected vision. It should be mentioned, how-

ever, that the ETDRS found that 5% of eyes had VA of <20/100 after 4 years of follow-up (ETDRS Research Group 1991a), compared to the 2% (2/81) of eyes with VA ≤ 0.1 found in our study.

Visual acuity outcome is dependent on macular function. In the present study, it was better among those in whom panretinal photocoagulation was instituted at the severe non-proliferative stage than among those in whom panretinal photocoagulation was instituted at the proliferative stage. The number of eyes that received focal and/or grid laser photocoagulation did not differ, indicating that exudative oedema occurred to similar extents in both groups. There were no other obvious reasons for visual loss, such as fibrous tissue in the vitreous or neovascular glaucoma in either of the groups. However, the possibility that ischaemic maculopathy had an influence on VA cannot be excluded and this could contribute to the slightly higher number of visually impaired eyes in the proliferative retinopathy group.

A previous study has shown that when comparing treatment outcome between type 1 and type 2 diabetes patients, patients with type 2 diabetes seem to benefit most from early treatment (i.e. treatment at the severe non-proliferative retinopathy stage) (Ferris 1996). These patients showed a 50% reduction in the rate of visual loss after early photocoagulation, in contrast to patients with type 1 diabetes, in whom no improvement in the rate of visual loss was seen. In our study of type 1 diabetes patients, laser treatment for severe non-proliferative retinopathy

seemed to be beneficial. The results may be partly explained by the fact that all our cases received treatment for exudative macular oedema prior to panretinal photocoagulation. In the ETDRS, eyes assigned to deferral of panretinal treatment did not receive any focal photocoagulation for macular oedema, until the positive results of macular treatment were released (ETDRS Research Group 1985). Furthermore, early treatment in our study referred only to eyes with severe non-proliferative retinopathy, whereas the early treatment group in the ETDRS also included eyes with early proliferative retinopathy.

The ETDRS stated that early panretinal photocoagulation should be considered but not immediately recommended, given its side effects of decreased peripheral and night vision (Frank 1975; Buckley et al. 1992). In cases where no early treatment was given, a maximum follow-up period of 2–3 months in patients with severe non-proliferative retinopathy was recommended. In our study, we showed that early laser treatment resulted in fewer vitreous haemorrhages and, possibly, fewer visually impaired eyes but side effects such as visual field defects, impaired night vision and contrast sensitivity were not studied. However, the psychological implications of, for example, frequent examinations, should also be taken into account. In a study comparing psychiatric symptomatology in patients with and without proliferative diabetic retinopathy, a strong correlation was seen between negative life events and recently diagnosed proliferative retinopathy. No such correlation was seen in patients treated with panretinal photocoagulation once the outcome was stabilized (Jacobson et al. 1985). Stabilization of diabetic retinopathy is probably more rapidly achieved at the severe non-proliferative stage and as the recommended follow-up time can be extended in properly treated patients (ETDRS Research Group 1991a), early panretinal photocoagulation might be psychologically beneficial.

Increased levels of baseline HbA_{1c} (Klein et al. 1994a; Davis et al. 1998) are associated with higher risks of developing more severe levels of retinopathy. In the present study, we found no differences in metabolic control between patients with severe

non-proliferative and proliferative retinopathy before photocoagulation or during the follow-up period. The present study used the mean of all HbA_{1c} values obtained during the observation period, thus reflecting the influence of longterm metabolic control, whereas only baseline values were used for analyses in the other studies (Klein et al. 1994a; Davis et al. 1998). In addition, neither blood pressure nor signs of nephropathy, both risk factors for retinopathy (Klein et al. 1989, 1993), differed between patients with severe non-proliferative or proliferative retinopathy. However, the lack of statistical significance in our study may well be due to the small numbers of patients.

The logistic regression analysis revealed no independent risk indicators predicting the development of new vessels in patients treated for severe non-proliferative retinopathy. This is in disagreement with other studies, which found progression of retinopathy to be determined by medical risk indicators such as metabolic control and hypertension (Klein et al. 1988, 1994b; Lloyd et al. 1995).

In summary, in this study of type 1 diabetes patients, treatment with panretinal photocoagulation for severe non-proliferative or proliferative retinopathy (in groups where age at onset and duration of diabetes, metabolic control and blood pressure levels were comparable) reduced the frequency of vitreous haemorrhages and vitrectomies in the severe non-proliferative group. The results indicate that panretinal photocoagulation might be beneficial as early as the severe non-proliferative retinopathy stage in type 1 diabetes patients.

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