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Research Article

Effect of Xenon Arc and Argon Laser Photocoagulation on Time to Blindness in Diabetic Retinopathy: A Survival Analysis of Paired-Eye Data

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Abstract

Background: Diabetic retinopathy is a leading cause of preventable blindness in adults of working age. Laser photocoagulation became the standard treatment after the Diabetic Retinopathy Study. **Aim:** To measure the effect of laser treatment on the time to blindness and to compare xenon arc with argon laser. **Methods:** The source dataset covers 200 patients. One eye of each patient was treated with laser and the other eye was left untreated. Blindness was defined as visual acuity below 5/200 on two consecutive visits. Survival was estimated with the Kaplan Meier method, compared with a log rank test within patients, and modelled with Cox regression. **Results:** Blindness occurred in 56 treated eyes (28.0%) and 101 untreated eyes (50.5%). At 48 months, 70.2% of treated eyes and 47.9% of untreated eyes were free of blindness. The hazard ratio for treated against untreated eyes was 0.41 (95% CI 0.28 to 0.59). The effect was larger in adult onset diabetes (HR 0.21) than in juvenile onset diabetes (HR 0.62). Xenon and argon gave similar results. **Conclusion:** Laser treatment roughly halved the hazard of blindness in this sample, with both laser types. The larger effect in adult onset diabetes needs confirmation.

1. Introduction

Diabetes is common and still increasing. The IDF Diabetes Atlas [1] reports 589 million adults aged 20 to 79 years living with diabetes and expects 853 million by 2050. About 22.27% of people with diabetes have diabetic retinopathy and 6.17% have the vision threatening form, and the number of adults with retinopathy is expected to reach about 160 million by 2045 [2]. In the proliferative stage, new fragile vessels grow on the retina, bleed, and can cause retinal detachment. Vision is usually kept until late, so the disease is often advanced when it is found [3].

The Diabetic Retinopathy Study (DRS) tested photocoagulation in patients with proliferative or severe nonproliferative retinopathy in both eyes. One eye of each patient was assigned to laser, using xenon arc or argon, and the other eye was followed without treatment. The main outcome was severe visual loss, meaning visual acuity below 5/200 at two consecutive visits [4]. Treatment lowered the risk by more than half, and both laser sources worked, although xenon caused more side effects such as loss of peripheral field [5, 6]. A later Cochrane review reached the same conclusion [7].

Anti VEGF injections are now an alternative to laser. Ranibizumab and aflibercept gave visual results comparable to panretinal photocoagulation in randomised trials [8, 9], yet laser is still part of current guidelines, mainly where regular injections are hard to provide [10, 11]. Because the two eyes of one patient share the same systemic factors, DRS data should be analysed with methods that respect the

pairing [12]. This study therefore reanalyses the paired data to measure the effect of laser on blindness and to see whether the effect depends on laser type or type of diabetes.

Aims

The aim of this study is to estimate the effect of laser photocoagulation on the time to blindness in diabetic retinopathy, using data in which one eye of each patient was treated and the other was not. The specific objectives are:

To describe the patients and the outcomes in treated and untreated eyes.
To compare survival free of blindness between treated and untreated eyes.
To estimate the hazard ratio for treatment, with and without adjustment for other variables.
To check whether the effect differs by laser type or type of diabetes.

2. Methodology

This is a secondary analysis of paired eye data. Within each patient, one eye was randomly assigned to laser and the other received no treatment, so every patient contributes one treated and one untreated eye. The source dataset has 200 patients: 101 were treated with xenon arc and 99 with argon laser, and the right eye was treated in 89 patients and the left eye in 111.

The event of interest was blindness, defined as the time from the start of treatment until visual acuity fell below 5/200 at two consecutive visits. Visits were three months apart, so the earliest possible event time is about 6.5 months. The times in the source dataset are the observed times minus 6.5 months and were used as given. Patients were censored at death, dropout, or the end of the study.

The source dataset was checked for missing values, duplicate identifiers, invalid codes and impossible times. None were found, except that three patients were coded as juvenile onset although they were 20 years or older at diagnosis. They were kept as coded. For the eye level analysis the data were rearranged to two rows per patient, giving 400 eyes.

Survival was estimated with the Kaplan Meier method [13] with 95% confidence intervals on the log log scale. Treated and untreated eyes were compared with a log rank test [14] in which each eye is compared only with its fellow eye. Hazard ratios were estimated with Cox regression [15]. A marginal model on the 400 eyes used treatment, laser type, age at diagnosis, type of diabetes and risk group, with standard errors clustered by patient [12]. A second model, stratified by patient, used only within patient contrasts, and a third added interaction terms for laser type and type of diabetes. The proportional hazards assumption was checked with Schoenfeld residuals [16]. All tests were two sided with a significance level of 0.05. About 59 events are needed to detect a hazard ratio of 0.48 with 80% power; the source dataset has 157.

Analysis was done in Python 3 (NumPy, SciPy, pandas, Matplotlib), with the survival routines written for this study. The data are anonymised and publicly listed, and no new patient data were collected.

3. Source Dataset, Details and License

The source dataset is titled “Diabetic retinopathy” and is hosted on Kaggle by the user cypcypDE. Its description names mayo.edu [17] as the source, and the data come from the Diabetic Retinopathy Study of the National Eye Institute. The same data are distributed as the diabetic dataset in the R package *survival* [18]. The source dataset has one sheet with 200 rows and 11 variables Table 1, no missing values, and a platform usability score of 2.94. No DOI, authors or update schedule are given.

Table 1: Variables in the source dataset

Variable	Meaning	Coding
id	Patient number	1 to 200
laser_type	Laser used in the treated eye	1 = xenon, 2 = argon
eye	Treated eye	1 = right, 2 = left
age	Age at diagnosis of diabetes	Years
type	Type of diabetes	1 = juvenile (under 20 years), 2 = adult
tr_group, untr_group	Risk group of treated and untreated eye	6 to 12
tr_status, untr_status	Outcome of treated and untreated eye	0 = censored, 1 = blindness
tr_time, untr_time	Follow up time of treated and untreated eye	Months (adjusted)

The license is listed as “Unknown” on the repository, so no reuse terms are stated. The source dataset was used only for non commercial academic analysis with credit to the source, and only summary results are reported. Permission from the rights holders should be obtained before the data are redistributed or used commercially.

4. Results

4.1. Patients

Mean age at diagnosis was 20.8 years (SD 14.7, range 1 to 58). Juvenile onset diabetes was found in 117 patients (58.5%) and adult onset in 83 (41.5%). The xenon and argon groups were similar Table 2 and Figure 1.

Table 2: Baseline characteristics by laser type

Characteristic	All (n = 200)	Xenon (n = 101)	Argon (n = 99)
Age at diagnosis, years, mean (SD)	20.8 (14.7)	22.1 (15.1)	19.5 (14.3)
Juvenile onset, n (%)	117 (58.5)	55 (54.5)	62 (62.6)
Adult onset, n (%)	83 (41.5)	46 (45.5)	37 (37.4)
Right eye treated, n (%)	89 (44.5)	48 (47.5)	41 (41.4)

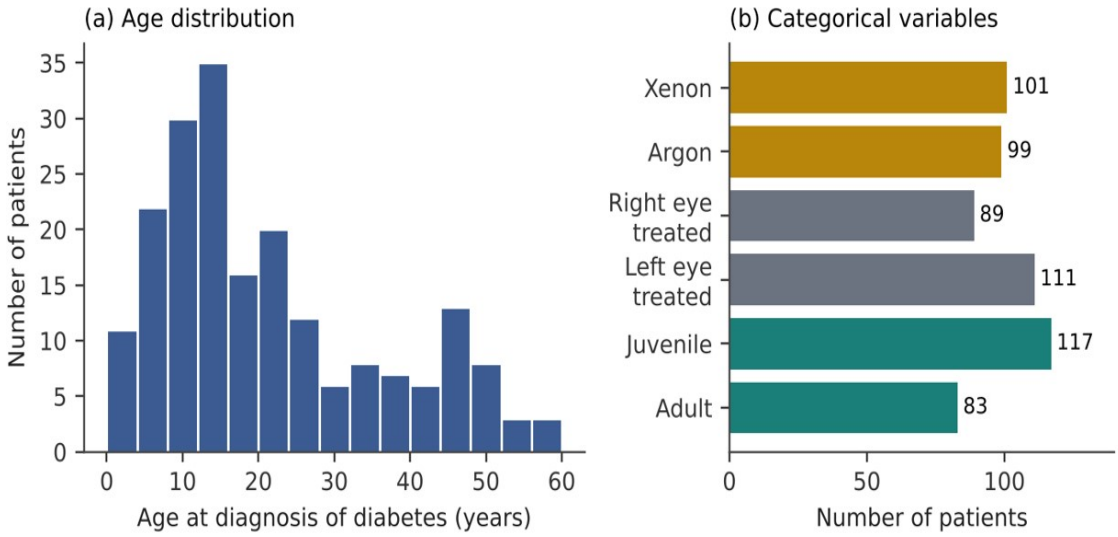


Figure 1: Age at diagnosis (a) and categorical characteristics (b) of the 200 patients

4.2. Blindness in treated and untreated eyes

Blindness occurred in 56 of 200 treated eyes (28.0%) and in 101 of 200 untreated eyes (50.5%) Table 3 and Figure 2. The median time to blindness in untreated eyes was 46.2 months. In treated eyes the median was not reached because the survival curve stayed above 0.5.

Table 3: Blindness and follow up by eye

Measure	Treated eye	Untreated eye
Blindness, n (%)	56 (28.0)	101 (50.5)
Censored, n (%)	144 (72.0)	99 (49.5)
Follow up, months, mean (SD)	38.6 (20.8)	32.4 (21.3)
Median time to blindness, months (95% CI)	Not reached	46.2 (33.6 to 61.8)

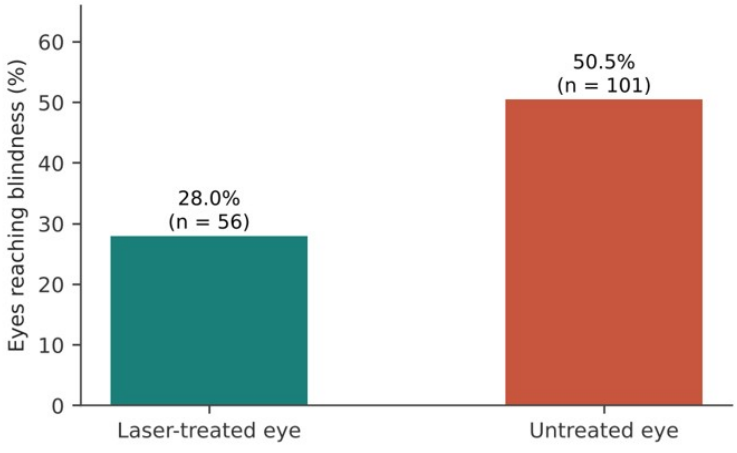


Figure 2: Percentage of eyes that reached blindness

4.3. Survival

The two curves separated early and stayed apart Figure 3. At 48 months, 70.2% of treated eyes and 47.9% of untreated eyes were free of blindness, a difference of about 22 percentage points Table 4. The log rank test within patients gave $\chi^2 = 24.86$ ($p < 0.001$).

Table 4: Probability of remaining free of blindness, % (95% CI)

Months since treatment	Treated eye	Untreated eye
12	88.2 (82.8 to 92.0)	78.6 (72.2 to 83.7)
24	80.2 (73.8 to 85.2)	63.9 (56.7 to 70.2)
36	73.9 (66.9 to 79.6)	56.7 (49.4 to 63.4)
48	70.2 (62.9 to 76.4)	47.9 (40.2 to 55.2)
60	69.3 (61.8 to 75.7)	42.0 (33.5 to 50.2)

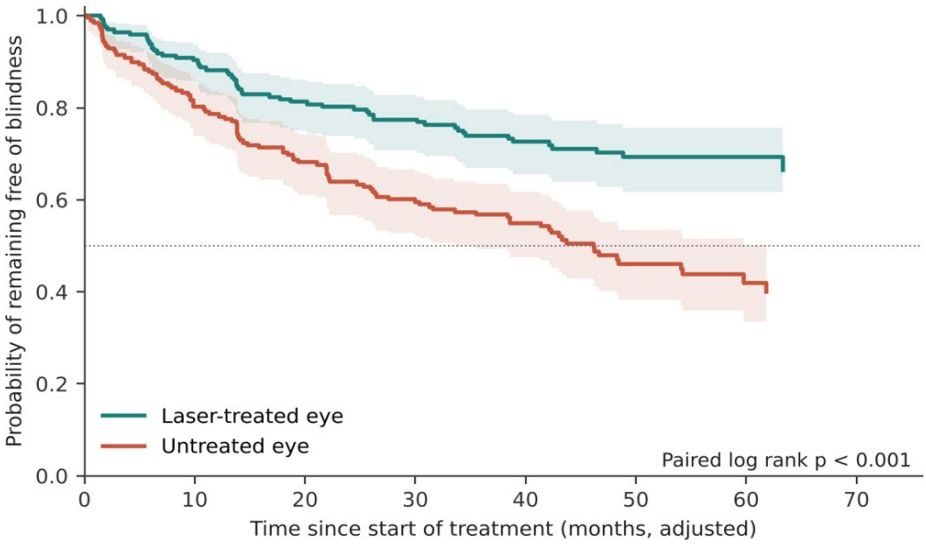


Figure 3: Kaplan Meier curves for time to blindness. Shaded bands are 95% confidence intervals

4.4. Treatment effect

The marginal Cox model gave a hazard ratio of 0.48 (95% CI 0.36 to 0.64) for treated against untreated eyes. In the model stratified by patient it was 0.41 (95% CI 0.28 to 0.59, $p < 0.001$). The effect was seen in every subgroup Table 5, Figure 4. It was similar for xenon (HR 0.43) and argon (HR 0.38), but larger in adult onset diabetes (HR 0.21) than in juvenile onset diabetes (HR 0.62). The interaction between treatment and adult onset was 0.34 (95% CI 0.15 to 0.75, $p = 0.008$), and the interaction with argon was not significant ($p = 0.65$).

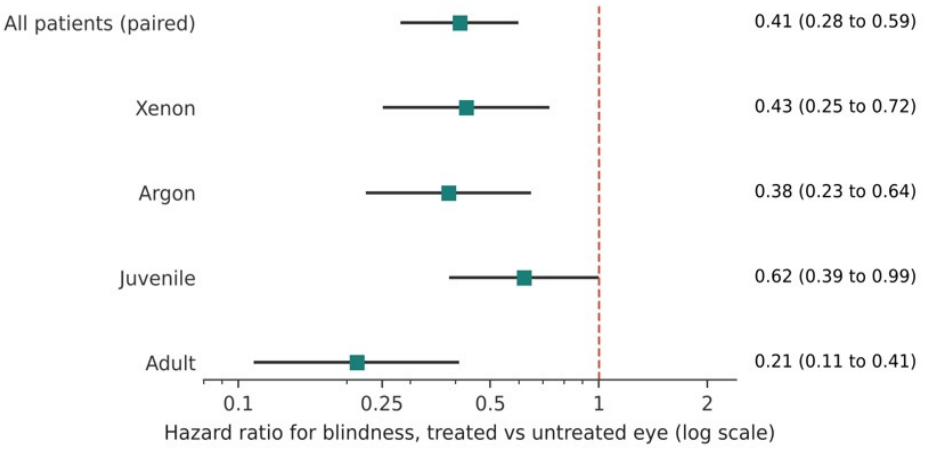


Figure 4: Hazard ratios for blindness overall and by subgroup. The dashed line marks no effect

Table 5: Hazard ratio for blindness, treated against untreated eye

Group	Patients	Events treated / untreated	HR (95% CI)	p
All patients	200	56 / 101	0.41 (0.28 to 0.59)	< 0.001
Xenon arc	101	25 / 51	0.43 (0.25 to 0.72)	0.002
Argon laser	99	31 / 50	0.38 (0.23 to 0.64)	< 0.001
Juvenile onset	117	38 / 51	0.62 (0.39 to 0.99)	0.044
Adult onset	83	18 / 50	0.21 (0.11 to 0.41)	< 0.001

HR from Cox models stratified by patient. For all patients the model was also adjusted for risk group.

4.5. Adjusted model

In the adjusted model, treatment stayed strongly protective (HR 0.47, 95% CI 0.35 to 0.64). Risk group was the only other variable clearly linked to blindness, with a 16% higher hazard for each extra unit (HR 1.16, 95% CI 1.03 to 1.30). Laser type, age and type of diabetes were not significant Table 6, Figure 5, and the proportional hazards assumption held (all $p > 0.20$). Among treated eyes only, argon and xenon did not differ (log rank p = 0.28; adjusted HR for argon 1.31, 95% CI 0.77 to 2.22).

Table 6: Adjusted Cox model (400 eyes, standard errors clustered by patient)

Variable	HR	95% CI	p
Laser treatment (vs none)	0.47	0.35 to 0.64	< 0.001
Argon laser (vs xenon)	1.22	0.87 to 1.73	0.251
Age at diagnosis (per year)	1.01	0.99 to 1.03	0.365
Adult onset (vs juvenile)	0.88	0.50 to 1.54	0.643
Risk group (per unit)	1.16	1.03 to 1.30	0.011

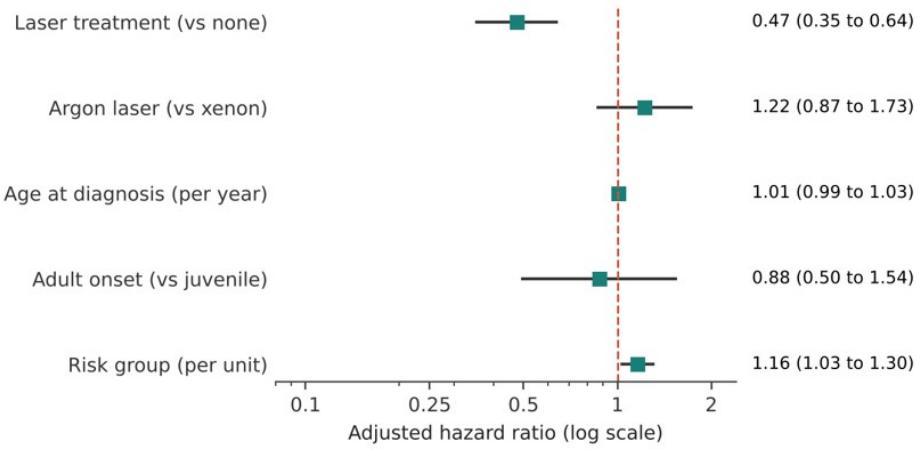


Figure 5: Adjusted hazard ratios with 95% confidence intervals

5. Discussion

Laser treatment clearly reduced blindness in this sample. About 28% of treated eyes and 50% of untreated eyes became blind, and the hazard ratio was 0.41 within patients and 0.48 in the marginal model. This agrees with the DRS finding of a risk reduction of more than half [5, 6] and with the Cochrane review [7]. The within patient estimate is the one the randomisation was built to support, because each treated eye is compared with its own fellow eye.

The effect was larger in adult onset diabetes. Among these patients 50 of 83 untreated eyes (60.2%) became blind against 18 of 83 treated eyes (21.7%), while among juvenile onset patients the figures were 51 of 117 (43.6%) and 38 of 117 (32.5%). Untreated adult onset eyes had the worst outlook, so they had more to gain. The source dataset cannot explain why, since blood pressure, glucose control and macular oedema were not recorded. This was one of several subgroup checks and should be confirmed in other data.

Xenon and argon did not differ, in line with the original DRS conclusion that both are effective [5]. The confidence interval for argon against xenon is wide (0.77 to 2.22), so a moderate difference cannot be excluded. A higher risk group score predicted blindness, as expected.

Anti VEGF drugs now compete with laser [8, 9]. These results do not argue against them. They show how high the risk of blindness is without treatment, which is the baseline any new treatment is measured against, and they support the continued use of laser where injections are difficult to deliver [11].

Limitations

- The study uses a secondary source dataset with few variables. It has no data on baseline visual acuity, blood sugar, blood pressure or macular oedema, and it does not say how the 200 patients were selected from the original trial.
- Event times are shifted by 6.5 months, so medians cannot be compared directly with studies that use observed times.
- The source dataset does not say whether any untreated eye was treated later, or why patients were censored. Later treatment of the control eye would make the effect look smaller, and dropout linked to poor vision could bias the curves.
- The subgroup results were not planned in advance and rest on fewer events, so the finding for adult onset diabetes is only suggestive.
- The survival routines were written for this study and were not checked in another package. The laser methods are also historical and differ from current practice.

6. Conclusions

In 200 patients with diabetic retinopathy, laser photocoagulation reduced the hazard of blindness by more than half (HR 0.41, 95% CI 0.28 to 0.59). At 48 months, 70.2% of treated eyes and 47.9% of untreated eyes were free of blindness. Xenon arc and argon laser performed similarly. The larger benefit in adult onset diabetes is a possible finding that needs confirmation.

Recommendations

- Keep laser treatment available for proliferative and severe nonproliferative retinopathy, especially where anti VEGF treatment and regular follow up cannot be ensured.
- Screen people with diabetes early, so that treatment is given while useful vision remains.
- Test the adult onset finding in the full DRS data and in recent cohorts.
- Repositories should state the license, the authors and how time variables were built, and studies of paired organs should analyse the pairing.

Article Information

Ethical Approval: The Institutional Ethics Committee of Babylon Education Directorate reviewed this retrospective study and determined that formal ethical approval was not required, as the research involved previously collected and anonymised clinical data.

Informed Consent: The requirement for informed consent was waived by the Institutional Ethics Committee.

Data Availability: The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest: The author declare that they have no conflict of interest.

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AI Use Disclosure: No generative artificial intelligence tools were used in the preparation of this manuscript.

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