Risk factors for sensation of pain during photocoagulation for diabetic retinopathy - a prospective observational study

Louise Kjærgaard Bystrup (louibyst@rm.dk)
Aarhus Universitetshospital https://orcid.org/0000-0002-2680-5136
Toke Bek
Aarhus Universitetshospital

Research article

Keywords: photocoagulation, pain, diabetic maculopathy, proliferative diabetic retinopathy

Posted Date: August 15th, 2019

DOI: https://doi.org/10.21203/rs.2.12951/v1

Abstract

Background Diabetic retinopathy can be treated by retinal photocoagulation. The treatment may induce discomfort and pain, and due to the individual variation of these adverse effects, it is a challenge to inform patients and to minimise discomfort during treatment. Methods The subjective sensation of pain was evaluated on a numeric rating scale from 0 – 10 in 235 successive patients receiving macular photocoagulation (MP) and 174 patients receiving panretinal photocoagulation (PRP). The influence of first/second eye, treatment session, gender, age, diabetic type, diabetic treatment, duration of diabetes, mean arterial pressure (MAP), body mass index (BMI), glycosylated haemoglobin (HbA1c), visual acuity, right/left eye, number, spot size and effect of applications on the perceived pain was studied. Results The pain score was significantly lower ($p<0.001$) after the first treatment in the first eye in patients treated with MP 1.67 ±1.8, n=235 (mean ±SD, n) than in patients treated with PRP 2.67 ±2.4, n=174 (mean ±SD, n). Lower mean arterial pressure, higher HbA1c and higher number and effect of the applications contributed significantly to increasing the reported pain during the first treatment in the first eye. For all patients treated in both eyes the reported pain was significantly ($p<0.001$) higher in the second 2.74 ±2.40, n=269 (mean ±SD, n) than in the first 2.08 ±2.14, n=269 (mean ±SD, n) eye. The pain was significantly higher during the two last than during the first treatment session in patients who received panretinal photocoagulation ($p<0.001$). Conclusions The higher pain during high treatment intensity and treatment in the retinal periphery might prompt a fractioning of treatment in patients with a low pain threshold. The increased pain with increasing HbA1c and decreasing MAP might be used to individualize information about treatment and to prepare health care professionals about the reactions of the patients.

Background

The introduction of antagonists to vascular endothelial growth factor (VEGF) has improved the prognosis for the treatment of retinal vascular diseases considerably (Oellers et al 2016, Virgili et al 2017, Mehta et al 2018), but retinal photocoagulation still has a role in the treatment of retinal ischaemic conditions such as in diabetic retinopathy (Figueira et al 2018). The mechanisms underlying the beneficial effect of retinal photocoagulation are not known in detail, but are assumed to be related to facilitation of diffusion from the choroid and elimination of the ischaemic tissue that releases growth factors (Stefánsson 2006).

Retinal photocoagulation may have long term side effects, such as constricted visual fields and reduced dark adaptation (Löwestam-Adrian et al 2003, Fong et al 2007), and the days immediately following treatment may be accompanied with blurred vision and photopsias (Bek & Erlandsen 2006). During treatment patients may experience discomfort and pain, and due to the individual variation of these side effects it is a challenge to inform patients and to prepare the treatment strategy to reduce these side effects. However, it is possible that the identification of risk factors for the development of side effects to retinal photocoagulation might reduce discomfort and facilitate the treatment procedure.

Therefore, the subjective sensation of pain was evaluated on a numeric rating scale (NRS) in 409 successive patients receiving retinal photocoagulation for diabetic retinopathy among which 235 patients

received macular and 174 panretinal photocoagulation. The contributions to the pain score of gender, age, diabetes type, treatment for diabetes, duration of diabetes mellitus, mean arterial pressure (MAP), body mass index (BMI), glycosylated hemoglobin (HbA1c), visual acuity, treatment type (macular/panretinal) and the number and effect of the photocoagulation applications were studied.

Methods

Patients

Five hundred and ninety-three patients comprising all patients from a population of approximately 0.9 million citizens who initiated retinal photocoagulation for diabetic retinopathy between March 9th 2011 and May 19th 2017, were studied. The patients were referred from private practitioning ophthalmologists and the regional screening clinic for diabetic retinopathy to the Department of Ophthalmology, Aarhus University Hospital, which is the only facility treating diabetic retinopathy in the area.

Examination

At referral, the patients were asked about the type of treatment for diabetes mellitus (insulin, oral antidiabetics, diet), diabetes type, and known onset of the disease as described previously (Mehlsen et al 2011). The arterial blood pressure (in mmHg) was measured twice (Omron M4-I, Omron, Matsusaka, Japan), and the mean arterial blood pressure (MAP) was calculated from the systolic (S) and diastolic (D) blood pressures as D + (S-D)/3, height (H) in cm and weight (W) in kg (SECA, Model 220, Hamburg, Germany) were used to calculate the body mass index (BMI) as W/H^2. Visual acuity was logarithmically transformed for the analysis.

Best corrected visual acuity was measured using ETDRS charts. Subsequently, the pupils were dilated using tropicamide 1% (Mydriacyl, Alcon, Puurs, Belgium) and phenylephrine 10% (Metaoxedrin, Hospital Pharmacy, Region Midtjylland, Denmark) eyedrops. Optical coherences tomography (OCT) scanning was performed using the Heidelberg Spectralis HRA+OCT apparatus (Version 1.7.0.0, Heidelberg, Germany) and fundus photography (Topcon TRC 50DX, Livermore, California, USA) was performed by the acquisition of two 50 degrees images, one centered on the optic disk and another on the fovea. Finally, the patient was evaluated by a retina specialist (TB) who initiated treatment if diabetic maculopathy (DM) defined in (Grauslund et al 2018) or proliferative diabetic retinopathy (PDR) defined in (Bek & Erlandsen 2006) were diagnosed. All patients with DM were treated with macular photocoagulation (MP) since the data was collected from before the initiation of anti-VEGF treatment for patients with center involving diabetic macular oedema. MP was performed using a (Visulas 532s, Carl Zeiss, Oberkochen, Germany) with a spot size of 300 microns, a duration of 0.1 seconds and with an effect that produced a definite whitening (Bek & Erlandsen 2006). Applications were positioned in a grid pattern inside the field of view of a Mainster lens corresponding to the retinal area containing retinopathy lesions, however sparing the papillomacular bundle and the retinal area within a half disk diameter temporal from the fovea. Panretinal photocoagulation (PRP) was performed in three sessions, the first being similar to that

of the MP, the second using a grid pattern to fill out the nasal hemiperiphery and the third treatment to fill out the temporal hemiperiphery. The number of applications, the spot size and effect used for the treatment were noted. All photocoagulation treatments were performed by the same person (TB), and immediately after each treatment session, the patient was asked to rate the perceived pain during treatment on a scale from 0 to 10 with 0 representing “no pain” and 10 representing a “maximum intolerable pain”. All clinical and epidemiological data were continuously entered into a database for surveillance of activity and quality assurance of the clinical activity. The nearest HbA1c value measured within 90 days of the first photocoagulation treatment was obtained from the central laboratory database.

The selection of patients for the analysis is shown in **Figure 1**. 125 patients were excluded because treatment had started before March 9. 2011 or because they had previously received treatment for diabetic retinopathy at another hospital during residence in another region. Four patients were excluded because they had received photocoagulation for other diseases than diabetic retinopathy, and 55 patients because of lack of pain score. Among the remaining 409 patients, 235 had received MP, 85 in one eye and 150 in both eyes, and 174 patients had received PRP, 55 in one eye and 119 in both eyes, 109 had completed three treatments in both eyes. The background data of the patients at the time of treatment in the first eye are shown in **Table 1**.

Table 1.

	First treatment	Macular	Panretinal
Variable	mean ±SD (n)	mean±SD (n)	mean±SD (n)
Gender (f/m)	153/256 (409)	92/143 (235)	61/113 (174)
Age (year)	55.5 ±14 (409)	59 ±13 (235)	50 ±15 (174)
Diabetes type (T1D/T2D)	123/286 (409)	43/192 (235)	80/94 (174)
Diabetes treatment (insulin/tablet/diet/ pancreas transplantation)	307/95/5/1 (408)	170/63/2/0 (235)	137/32/3/1 (173)
Diabetes duration (year)	17 ±10 (409)	15 ±10 (235)	19 ±11 (174)
MAP (mmHg)	101 ±13 (362)	101 ±12 (224)	101 ±15 (138)
BMI (kg/m^2)	29 ±6 (338)	30 ±6 (218)	28 ±6 (120)
HbA1c (mmol/mol)	67 ±17 (362)	65 ±14 (214)	69 ±17 (148)
HbA1c_time (days)	0.8 ±37 (362)	-2.5 ±37 (214)	5.5 ±35 (148)
Visual acuity, logMAR	0.15 ±0.26 (409)	0.13 ±0.24 (235)	0.18 ±0.28(174)
Treatment variables			
Side (right/left eye)	275/134 (409)	163/72 (235)	112/62 (174)
Applications (numbers)	499 ±259 (409)	396 ±237 (235)	638 ±220 (174)
Effect (mW)	245 ±29 (409)	245 ±29 (235)	244 ±30 (174)
Spot size (200/300 micrometers)	296 ±21 (409)	296 ±20 (235)	296 ±21 (174)
Treatment (macular/panretinal)	235/174 (409)	-	-

The background variables at the time of first treatment in the first eye.

Statistical analysis

All analyses were performed in STATA (version 15.0, StataCorp, Texas, USA). Test for normal distribution was performed by QQ plots and histograms. The univariate proportion of the variables was studied using means and t-tests.

Unpaired t-test was used to test differences between reported pain in the first eye receiving MP and PRP. Multiple linear regression was used to study the influence of age, duration of diabetes, MAP, BMI, HbA1c, number, spot size and effect of applications, visual acuity, gender, diabetes type, diabetic treatment, right/left eye, the type of photocoagulation treatment (macular/panretinal) – on the reported pain at the first treatment session.

Paired t-test was used to test differences in reported pain and number of applications between first and second eye in patients who had bilateral treatment.

Repeated measures two-way analysis of variance (ANOVA) was used to test differences in reported pain between the three treatment sessions in eyes receiving PRP.

Results

At the first photocoagulation in the first eye the pain score was 2.1 ±2.1, 409 (mean ±SD, n) in all patients, but was significantly lower ($p<0.001$) in patients treated with MP (1.67 ±1.8, 235) than in patients treated with PRP (2.67 ±2.4, n=174).

The variables included in the multiple linear regression contributed with 21 % (adjusted R-square) to the variation in the reported pain. **Table 2** shows that lower mean arterial pressure, higher HbA1c and higher number and effect of the applications contributed significantly to increasing the reported pain during the first treatment in the first eye (n=295).

For all patients treated in both eyes the reported pain was significantly higher ($p<0.001$) in the second 2.74 ±2.40, 269 (mean ±SD, n) than in the first eye (2.08 ±2.14, 269), which was due to a significantly ($p<0.001$) higher reported pain in the second eye (2.53 ±2.30, n=150) than in the first eye (1.61 ±1.76, n=150) in patients treated with MP, but not in patients treated with PRP. There was no significant difference in the number of applications given at the first photocoagulation in the first and second eye.

Table 2.

Variable (n=295)	Coef.	95% CI	p
Gender (f/m)	-0.40	[-0.85; 0.04]	0.077
Age (year)	-0.003	[-0.03; 0.02]	0.809
Diabetes type (T1D/T2D)	-0.22	[-0.98; 0.54]	0.567
Diabetes treatment (insulin/tablet/diet/pancreatic transplantation)	0.1	[-0.41; 0.62]	0.691
Diabetes duration (years)	0.01	[-0.02; 0.04]	0.437
MAP (mmHg)	-0.02	[-0.04; -0.001]	0.038*
BMI (kg/m^2)	0.02	[-0.02; 0.06]	0.358
HbA1c (mmol/mol)	0.02	[0.002; 0.03]	0.022*
logMAR	0.09	[-0.79; 0.98]	0.836
Treatment variables			
Side (right/left eye)	0.19	[-0.27; 0.65]	0.412
Applications	0.003	[0.002; 0.004]	0.000*
Effect (mW)	0.01	[0.001; 0.02]	0.036*
Spot size (my)	0.01	[-0.005; 0.02]	0.289
Treatment (macular/panretinal)	0.17	[-0.38; 0.7]	0.544

Coefficients, 95% confidence intervals and p-values from the multiple linear regression of the background variables at first treatment of first eye contributing to reported pain.

Figure 2 shows that in patients who received PRP the reported pain was significantly higher at the two last than at the first treatment session ($p<0.001$).

Discussion

The present study is the first to report risk factors for the subjective sensation of pain during photocoagulation for diabetic retinopathy. The design of the study was strong by including all photocoagulation treatments for diabetic retinopathy performed on citizens within a defined time and geographical area. Data were only missing in few cases where the collection of pain scores had been considered to be unreliable because communication with the patient had been indirect such as through an interpreter. For the collection of pain a visual analogue scale was considered, but ultimately a numerical rating scale (NRS) was selected because the results of this approach has been shown to be more easy to use and interpret (Paice and Cohen 1997).

The study of the subjective sensation of pain during treatment for diabetic retinopathy is relevant since diabetic patients may have neuropathy that reduces the sensation of pain (Kärvestedt et al 2011) which may modify the need for information about the course and consequences of treatment. Topical anaesthesia used to alleviate discomfort from the contact lens used for treatment may be reduced in

diabetic patients because of reduced corneal sensitivity (Markoulli et al 2018), but cannot be expected to reduce pain induced by photocoagulation in the retina (Ramezani et al 2017).

In previous studies the influence of stimulus duration (Mirshahi et al 2013) and different modes of stimulus application (Inan et al 2016) on the subjective sensation of pain during photocoagulation for diabetic retinopathy have been investigated. However, in these studies the treatments were not standardised to allow an evaluation of the influence of different treatment sessions, to differentiate between treatment for diabetic maculopathy and proliferative diabetic retinopathy, and background parameters that might influence the sensation of pain were not considered.

The variables included in the multiple linear regression in the present study could only explain 21 % of the variation in pain score implying that not all factors related to the sensation of pain had been included in the analysis. These factors might be related to individual differences in pain threshold. The number and effect of the photocoagulation applications during the first treatment reflect the energy impinging on the retina, and the association of higher energy with higher sensation of pain is therefore obvious. The finding that DM patients experienced more pain during treatment in the second eye than in the first eye is suggestive, but may be related to differences in retinopathy among the two eyes that had influenced the choice of the first eye to be treated. The significant higher pain reported after the second and the third treatment sessions than after the first session in patients receiving PRP may be related to the higher number of applications given in the retinal periphery. However, it is likely that differences in sensitivity between the macular area and the retinal periphery may also have played a role. However, the relative contribution of the number of applications and the treatment zone to the perceived pain cannot be assessed from the results of the present study.

The fact that increasing HbA1c and decreasing mean arterial blood pressure (MAP) were found to increase the subjective sensation of pain during photocoagulation treatment remains to be explained. The finding might be related to factors sensitizing the patients to pain that are not included in the study, such as e.g. medication, or might reflect a direct relation between pain threshold, blood pressure and metabolic regulation (Gibbons et al 2010).

Altogether, the present study has contributed new evidence to explain what factors influence pain during photocoagulation for diabetic retinopathy. The higher pain during high treatment intensity and treatment in the retinal periphery might prompt a fractioning of the treatment in patients with a low pain threshold. Additionally, the increased pain with increasing HbA1c and decreasing MAP might be used to individualize information about treatment and to prepare health care professionals for the reactions of the patients during photocoagulation for diabetic retinopathy.

Conclusions

The pain induced by photocoagulation for diabetic retinopathy correlates with the intensity of the applications. Treatment in the retinal periphery should prompt a fractioning of treatment to more sessions in patients with a low pain threshold. The increased pain with increasing HbA1c and decreasing

mean arterial blood pressure might be used to individualize information about treatment and to alert health care professionals about patients who may respond adversely to treatment.

List Of Abbreviations

macular photocoagulation (MP)

panretinal photocoagulation (PRP)

mean arterial pressure (MAP)

body mass index (BMI)

glycosylated hemoglobin (HbA1c)

standars deviation (SD)

number (n)

vascular endothelial growth factor (VEGF)

numeric rating scale (NRS)

systolic blood pressure (S)

diastolic blood pressure (D)

height (H)

weight (W)

early treatment diabetic retinopathy study (ETDRS)

Toke Bek (TB)

diabetic maculopathy (DM)

proliferative diabetic retinopathy (PDR)

analysis of variance (ANOVA)

Declarations

Ethics approval

The project has been presented for The Central Denmark Region Comittees on Health Research Ethics. According to the Consolidation Act on Research Ethics Review of Health Research Projects, Consolidation Act number 1083 of 15 September 2017, section 14(2) notification of questionnaire surveys or medical database research projects to the research ethics committee system is only required if the project involves human biological material. The study may be conducted without an approval from the Committees.

Consent to participate

As part of the routines in the department patients gave written and oral consent to participate, and the signature on the consent page was scanned into the electronic patient record.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by Fight for Sight, Denmark. Funding for salary to carry out the analyses.

Authors contributions

TB examined and treated all patients and registered data. LB collected, analysed and interpreted all data. LB and TB were both major contributors in the interpretation and writing the manuscript. Both authors read and approved the final manuscript.

Acknowledgements

Not applicable.

References

Bek T, Erlandsen M. Visual prognosis after panretinal photocoagulation for proliferative diabetic retinopathy. Acta Ophthalmol 2006;84/1:16-20.

Figueira J, Fletcher E, Massin P, Silva R, Bandello F, Midena E, Varano M, Sivaprasad S, Eleftheriadis H, Menon G, Amaro M, Ayello Scheer S, Creuzot-Garcher C, Nascimento J, Alves D, Nunes S, Lobo C, Cunha-Vaz J, EViCR.net Study Group. Ranibizumab plus panretinal photocoagulation versus panretinal photocoagulation alone for high-risk proliferative diabetic retinopathy (PROTEUS Study). Ophthalmology 2018;125/5:691-700.

Fong DS, Girach A, Boney A. Visual side effects of successful scatter laser photocoagulation surgery for proliferative diabetic retinopathy: a literature review. RETINA 2007;27/7:816-24.

Gibbons CH, Freeman R. Treatment-induced diabetic neuropathy: a reversible painful autonomic neuropathy. Ann Neurol 2010;67/4:534-41.

Grauslund J, Andersen N, Andresen J, Flesner P, Haamann P, Heegaard S, Larsen M, Laugesen CS, Schielke K, Skov J, Bek T. Evidence-based Danish guidelines for screening of diabetic retinopathy. Acta Ophthalmol 2018 Oct 11. doi: 10.1111/aos.13936. [Epub ahead of print]

Inan UU, Polat O, Inan S, Yigit S, Baysal Z. Comparison of pain scores between patients undergoing panratinal photocoagulation using navigated or pattern scan laser systems. Arg Bras Oftalmol 2016;79/1:15-8 .

Kärvestedt L, Mårtensson E, Grill V, Elofsson S, von Wendt G, Hamsten A, Brismar K. The prevalence of peripheral neuropathy in a population-based study of patients with type 2 diabetes in Sweden. J Diabetes Complications. 2011;25/2:97-106.

Lovestam-Adrian M, Agardh CD, Torffvit T & Agardh E: Type 1 diabetes patients with severe non-proliferative retinopathy may benefit from panretinal photocoagulation. Acta Ophthalmol Scand 2003;81/3: 221–225.

Markoulli M, Flanagan J, Tummanapalli SS, Wu J, Willcox M. The impact of diabetes on corneal nerve morphology and ocular surface integrity. Ocul Surf 2018;16/1:45-57.

Mehlsen J, Erlandsen M, Poulsen PL, Bek T. Identification of independent risk factors for the development of diabetic retinopathy requiring treatment. Acta Ophthalmol 2011;89/6:515-21.

Mehta H, Tufail A, Daien V, Lee AY, Nguyen V, Ozturk M, Barthelmes D, Gillies MC. Real-world outcomes in patients with neovascular age-related macular degeneration treated with intravitreal vascular endothelial growth factor inhibitors. Prog Retin Eye Res 2018;65:127-46.

Mirshahi A, Lshay A, Roozbahani M, Fard MA, Molaie S, Mireshghi M, Zaferani MM. Pain score of patients undergoing single spot, short pulse laser versus conventional laser for diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol 2013;251/4:1103-7.

Nascimento VP, Primiano HP Jr, Maia OO Jr et al. Analgesic effect of etoricoxib (Arcoxia®) 120 mg during retinal laser photocoagulation. Eur J Ophtalmol. 2012;22/3:388-92.

Oellers P, Grewal DS, Fekrat S. Role of aflibercept for macular edema following branch retinal vein occlusion: comparison of clinical trials. Clin Ophthalmol 2016;8/10:411-8.

Paice JA, Cohen FL. Validty of a verbally administered numeric rating scale to measure cancer pain intensity. Cancer Nurs. 1997;20/2:88-93.

Ramezani A, Entezari M, Shahbazi MM, Semnani Y, Nikkhah H, Yaseri M. Analgesic Effect of Topical Sodium Diclofenac before Retinal Photocoagulation for Diabetic Retinopathy: A Randomized Double-masked Placebo-controlled Intraindividual Crossover Clinical Trial. Korean J Ophthalmol. 2017;31/2:102-107.

Stefansson E. Ocular oxygenation and the treatment of diabetic retinopathy. Surv Ophthalmol 2006;51/4:364-80.

Virgili G, Parravano M, Evans Jr, Gordon I, Lucenteforte E. Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis. Cochrane Database Syst 2017 Jun 22;6:CD007419. doi: 10.1002/14651858.CD007419.pub5. Review.

Figures

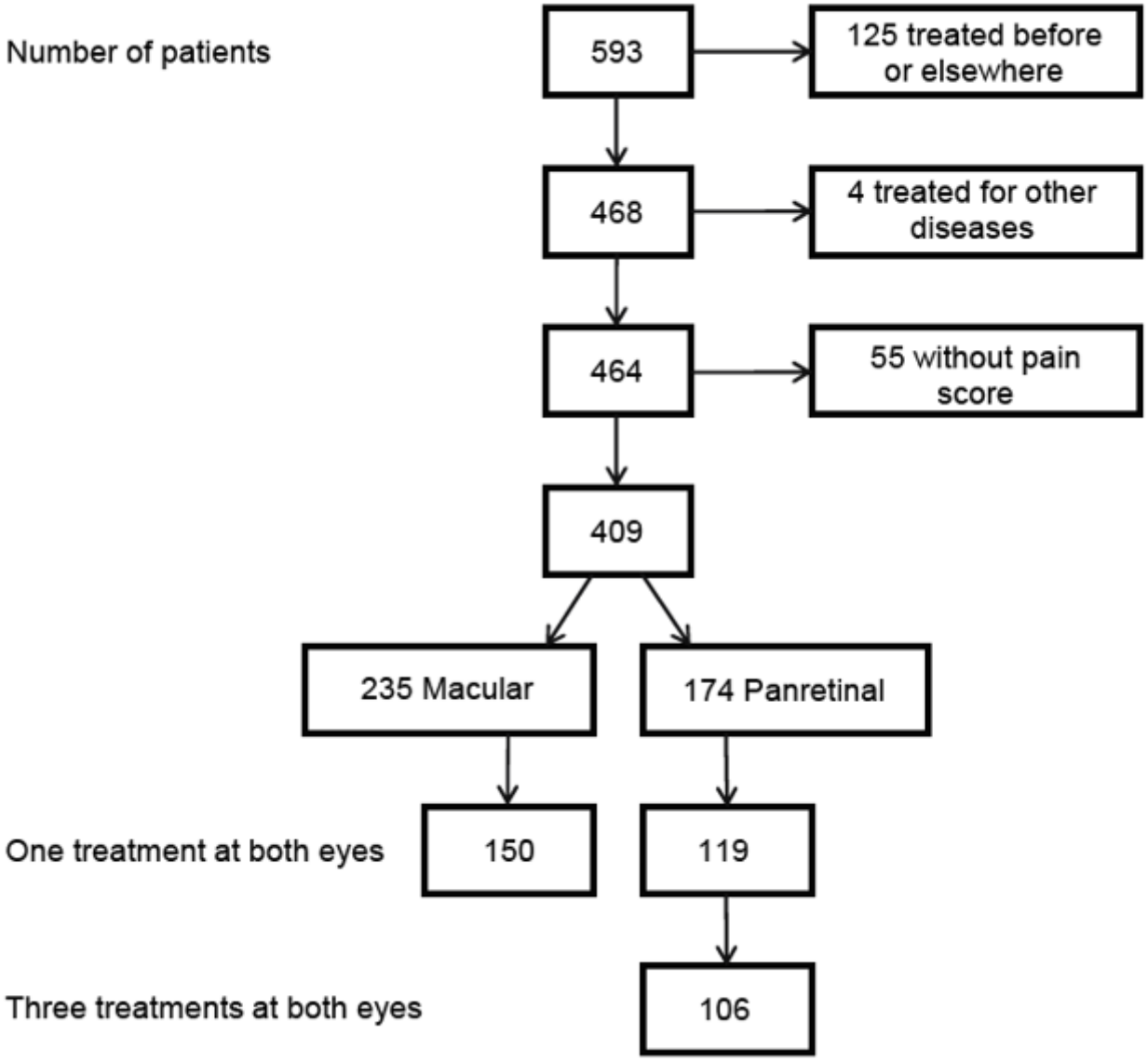

Figure 1

The patient selection

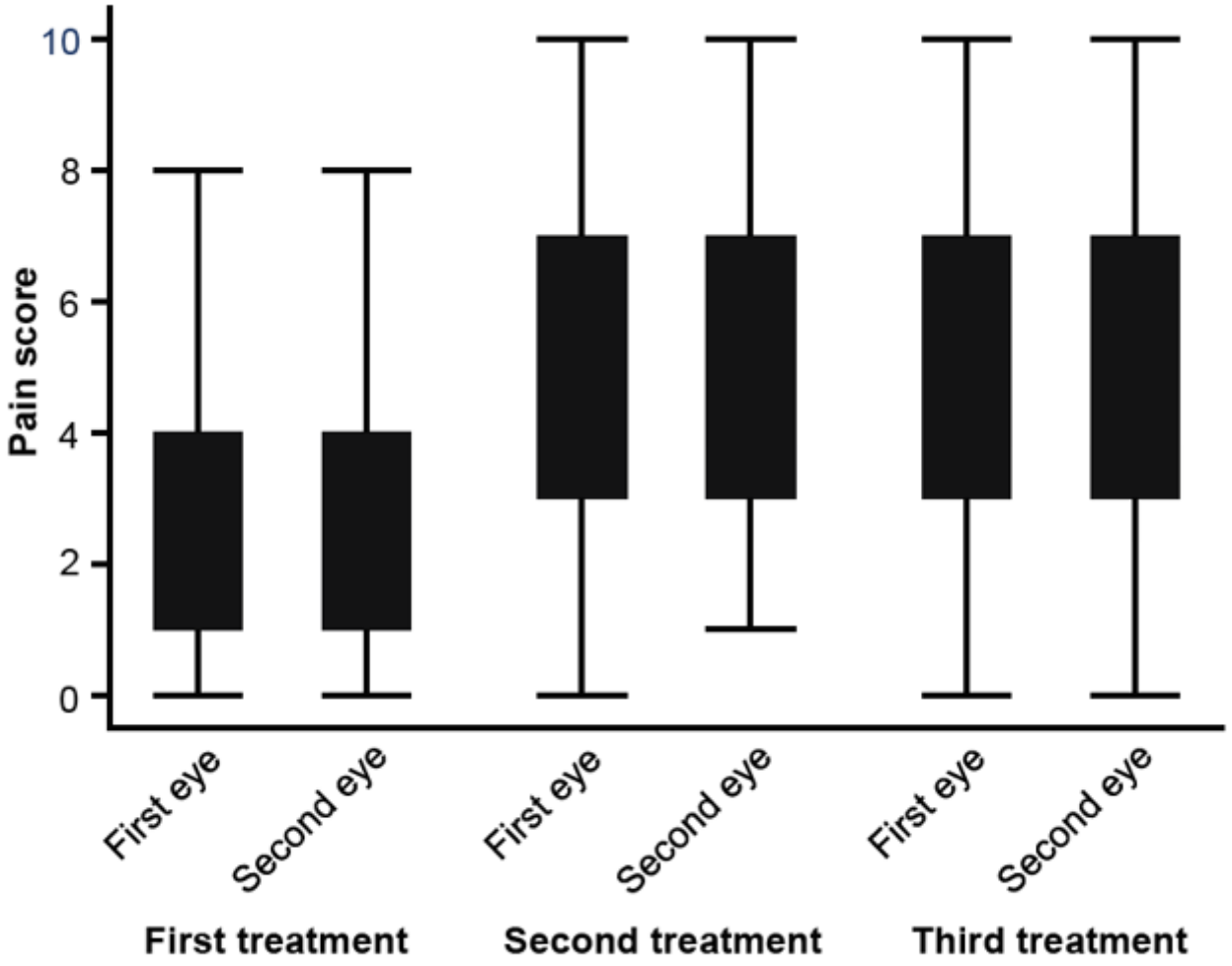

Figure 2

The reported pain in the first and second eye in the three sessions of panretinal photocoagulation