Prospective randomised controlled trial comparing sub-threshold micropulse diode laser photocoagulation and conventional green laser for clinically significant diabetic macular oedema

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Prospective randomised controlled trial comparing sub-threshold micropulse diode laser photocoagulation and conventional green laser for clinically significant diabetic macular oedema

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ABSTRACT

Aim: The study was a prospective randomised controlled double-masked trial performed in two centres to compare sub-threshold micropulse diode laser photocoagulation (MPDL) with conventional green laser photocoagulation (CGL) in the treatment of clinically significant diabetic macular oedema (CSMO).

Methods: Fifty-three patients (84 eyes) with diabetic CSMO were randomly assigned to MPDL (n = 44) or CGL (n = 40) according to the modified Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. Treatments were performed after baseline and re-treatments were allowed at or after the 4 month visit if necessary. Parameters noted included the best corrected visual acuity (BCVA), colour fundus photographs, central retinal thickness using optical coherence tomography (OCT), vision contrast sensitivity with Pelli–Robson charts and presence of visible laser scars at baseline and at 4 and 12 months. The primary outcome was BCVA at 12 months.

Results: All patients completed 12 months of follow-up after treatment at baseline. There were no statistically significant differences in BCVA, contrast sensitivity and retinal thickness between the two laser modalities at 0, 4 and 12 months. We found that laser scarring was much more apparent with CGL than with the sub-threshold approach (MPDL). Laser scars were identified at the 12 month visits in 13.9% of the MPDL-treated eyes compared with 59.0% of the CGL-treated eyes ($p<0.001$).

Conclusion: Sub-threshold micropulse diode laser photocoagulation is equally as effective as CGL treatment for CSMO.

Trial registration number: ISTRN 90646644.

Macular oedema affects approximately 29% of diabetic patients with disease duration of 20 years or more and remains the most frequent cause of visual loss in those patients.[1]

The Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated that laser photocoagulation applied to patients with clinical significant diabetic macular oedema (CSMO) reduced the incidence of visual loss by approximately 50% at 3-year follow-up.[2]

The conventional green laser (CGL) treatment is applied in a focal or grid pattern and produces a visible burn in the retina. Enlargement of laser scars after treatment has been reported.[3]

Sub-threshold micropulse diode laser (MPDL) has recently been shown to be effective in the treatment of CSMO and seems to have a theoretical advantage, since the laser burns will affect deeper layers with relative sparing of the inner neurosensory retina, thus reducing the scarring and paracentral scotomas post-treatment.[4]

We conducted a prospective randomised double-masked interventional controlled trial at two centres, comparing the efficacy and side effects of these two types of laser treatment for diabetic CSMO.

MATERIAL AND METHODS

This study included 84 eyes from 53 type 2 diabetic patients with CSMO (as defined by ETDRS study) in two centres: Coimbra (Portugal) with 21 patients (42 eyes) and London (UK) with 32 patients (42 eyes).

Our study population included patients less than 80 years old, with type 2 diabetes and with both eyes fulfilling the ETDRS criteria for CSMO, based on stereo fundus photography and best corrected visual acuity (BCVA) of ⩾55 letters on the modified ETDRS chart (equivalent to 20/80 or better).

Exclusion criteria were as follows:

- Any previous retinal laser treatment
- Proliferative diabetic retinopathy
- Rubeosis
- Foveal avascular zone (FAZ) disrupted by capillary closure in more than 30% of the central circle on the fluorescein angiography
- Glaucoma (visual field alteration or intraocular pressure greater than 29 mmHg)
- Significant cataract (which does not allow complete ocular examination and proposed measurements)
- Pseudophakic eyes with surgery within 1 year before enrolment
- Other intra-ocular surgery other than cataract
- Dilation of pupil less than 5 mm
- Other retinal vascular diseases
- Any condition that might interfere with assessment of the progression of macular oedema
- Brittle diabetes (ie persons who report decompensation in their glycaemic control, with recurrent ketoacidosis or hypoglycaemia)

- Haemoglobin A_{1c} (HbA_{1c}) levels >11%
- Impaired renal function demonstrated by receiving dialysis
- Uncontrolled hypertension showing values of blood pressure greater than 90 mmHg (diastolic blood pressure (BP)) or >165 mmHg (systolic BP)
- Patients who had received any investigational drug or device within 4 weeks prior to screening.

We randomised the eyes into two treatment groups according to a randomisation table. A total of 40 eyes received CGL and 44 eyes received MPDL. Patients with bilateral CSMO were randomised in order to receive CGL in one eye and MPDL in the other eye.

Patients were examined at baseline (V0), month 4 (V4) and month 12 (V12) visits. Each visit included an ophthalmological examination with BCVA, refraction, contrast sensitivity testing, slit-lamp examination, tonometry and ophthalmoscopy. The following examinations were also performed: seven-fields digital stereo fundus photography (30°) and thickness measurements by optical coherence tomography (OCT). Fluorescein angiography, BP and HbA_{1c} values were also obtained at baseline and as required.

Prior to photocoagulation, treatment maps for each eye were prepared on acetate sheets over fundus photography, based on stereo fundus photography and fluorescein angiography. The CGL treatment protocol was similar to that of the ETDRS treatment, but was modified using lower power to just visible. For the eyes that received MPDL, the area of oedema was outlined in the treatment map in a grid pattern over the leaking or capillary occlusion area while sparing the centre of the FAZ.

Treatment technique

Under pupillary dilatation and topical anaesthesia, eyes were photocoagulated using the Volk Area Centralis contact lens (Volks Optical Inc, Mentor, Ohio, USA) according to the randomisation table and based on the treatment maps. All the laser treatments were undertaken within 1 month of the baseline visit.

The CGL was performed with a 514 nm argon green laser light using the Coherent Novus 2000 (Coherent, Santa Clara, California, USA) in Coimbra and Iridex Oculite GLx (Iridex Corp., Mountain View, California, USA) in London. We used 100 and 200 μm spot sizes with an exposure time of 100 ms in Coimbra and 125 μm spot size with an exposure time of 100 ms in London. The power was adjusted by slowly increasing the laser power until a light grey-white (just visible) burn was obtained; it was applied in a focal or grid pattern according to the treatment map.

The eyes randomised to receive MPDL were treated with laser light at 810 nm using a Iridex Oculite SLx (Iridex Corp.) diode laser. A first test laser burn with 125 μm spot size and continuous wave laser of 300 ms was applied outside the arcade and the power was increased until a visible laser burn was seen. The diode laser was then changed to the micropulse mode with a 15% duty cycle and the power to achieve the visible laser burn doubled. Finally, treatment was applied to the area of oedema according to the treatment maps, without visible burns in the retina.

When necessary, re-treatments were performed at or after the 4-month visit. In those cases new treatment maps for re-treatment were made.

Outcome measures

The primary outcome measure was the BCVA using the ETDRS letter scores recorded in a masked manner at 12 months after the laser treatment. Secondary endpoints were change in the central macular thickness, contrast vision sensitivity and presence of macular laser scars.

The central retina thickness was defined as the average thickness of the central macular region, 1000 μm diameter, centred on the patient's fovea, and automatically measured by the Stratus OCT-3 (Humphrey Instruments Inc., Dublin, California, USA) using the fast macular thickness mapping protocol with software version 4.0.

The Pelli–Robson contrast sensitivity test was performed using the two charts (one for each eye) at a distance of 1 m, before dilating the pupil and wearing the best correction lens for distance.

A masked observer reviewed all the colour fundus images at the 12-month follow-up visit in order to identify laser scars at macular area, without knowing the treatment performed in those eyes.

Data analysis

The following parameters were considered: visual acuity, contrast sensitivity, retinal thickness and development of visible laser scars.

The parameters were analysed according to their mean values at each visit (V0, V4 and V12) and their change in the 1-year follow-up period.

To select the most appropriate statistical tests, the normality, variance and outliers for each parameter at each visit were analysed. For that purpose, the Kolmogorov–Smirnov test was used for the assessment of the normality of data.

Statistical significant differences between the CGL and the MPDL groups were tested with the Mann–Whitney test. Statistical significant differences between visits for the CGL and the MPDL group were tested by the Friedman test (for the three follow-up visits) and/or the Wilcoxon test (for two visits, ie from V0 to V4, from V4 to V12 and from V0 to V12). For categorical data the chi-square test (Pearson chi-square) was used to assess statistical significance between categories. Correlation was performed using the Spearman correlation coefficient. The odds ratio was computed to compare the relative risk for visible laser scars in the CGL and in the MPDL groups.

Statistical analysis was performed using SPSS software (version 13.0 for Windows) (SPSS LEADS Technologies, Inc., Chicago, Illinois, USA).

RESULTS

Of the 53 patients, 32 were men and 21 were women, and all of them completed the 12 months of follow-up. The mean age was 60.5 (SD 9.8) (range 34 to 78) years. The mean duration of diabetes was 12.4 (SD 5.56) years. The mean HbA_{1c} at baseline visit was 9.0% (SD 1.5%).

No statistical significant differences between the two laser groups were found between parameters at baseline visit ($p>0.10$) (table 1). The non-statistically significant difference between groups was also verified within the two centres ($p = 0.067$).

Visual acuity

Initial mean BCVA was 78.4 (SD 8.1) letters in MPDL group and 78.0 (SD 7.8) letters in CGL group. The mean visual acuity was 77.2 (SD 10.4) letters and 75.0 (SD 13.7) letters at 4 and 12 months, respectively, in MPDL eyes; the mean visual acuity

Table 1 Baseline clinical characteristics of the two groups

Characteristic	CGL group (n = 40)	MPDL group (n = 44)
Age (years)	61.1 (9.9)	59.8 (9.9)
Diabetes duration (years)	12.4 (5.7)	12.4 (5.6)
HbA_{1c} (%)	9.1 (1.6)	9.0 (1.6)
Diastolic blood pressure (mmHg)	136.1 (26.4)	134.3 (26.1)
Systolic blood pressure (mmHg)	78.1 (8.9)	77.4 (9.1)
BCVA (letters)	78.0 (7.8)	78.4 (8.1)
Contrast sensitivity (letters)	31.2 (3.4)	31.1 (3.1)
Central retina thickness (μm)	255.0 (61.9)	248.9 (58.7)

Values are mean (SD).
BCVA, best corrected visual acuity; CGL, conventional green laser; MPDL, micropulse diode laser.

was 76.1 (SD 12.8) letters and 72.5 (SD 17.1) letters, respectively, in CGL eyes.

No statistical significant differences in the mean visual acuity value were found at V0, V4 and V12 between the CGL and MPDL groups (p = 0.81) (fig 1). There was also no statistical difference in change in BCVA at 12 months between the two laser groups (−7.3 ETDRS letters in CGL group compared with −6.6 letters in MPDL group; p = 0.88)

Macular thickness

Initial mean central macular thickness was slightly higher in the CGL group (255.0 (SD 61.9) μm) compared with MPDL (248.9 (SD 58.7) μm), but no statistical significant difference was found (p = 0.87).

From baseline to V12 there was an increase in central macular thickness of 28.7 (SD 105.3) μm and 41.9 (SD 103.8) μm for the CGL and MPDL groups, respectively. No statistical significant difference was found between the two groups for the changes from V0 to V4 and from V0 to V12 (p = 0.81) (fig 2).

Contrast vision sensitivity

Initial mean contrast sensitivity was 31.2 (SD 3.4) letters in CGL group and 31.1 (SD 3.1) letters in MPDL group. The mean contrast sensitivity at 4 and 12 months was 31.4 (SD 3.1) letters and 30.8 (SD 8.5) letters, respectively, in CGL-treated eyes; the mean contrast sensitivity was 31.9 (SD 3.1) letters and 30.2 (SD 4.3) letters, respectively, in MPDL-treated eyes.

No statistical significant differences in the mean contrast vision values were found for all of the visits between the CGL and MPDL groups (p = 0.87).

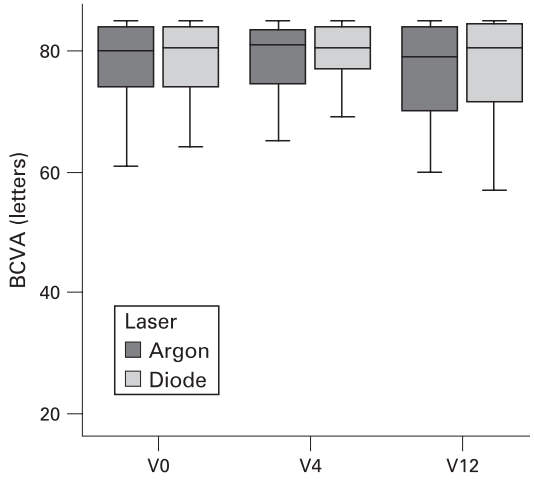

Figure 1 Boxplot (median and interquartile values) for best corrected visual acuity (BCVA) at baseline (V0), 4 months (V4) and 12 months (V12). Vision was better preserved in MPDL eyes but the difference was not significant.

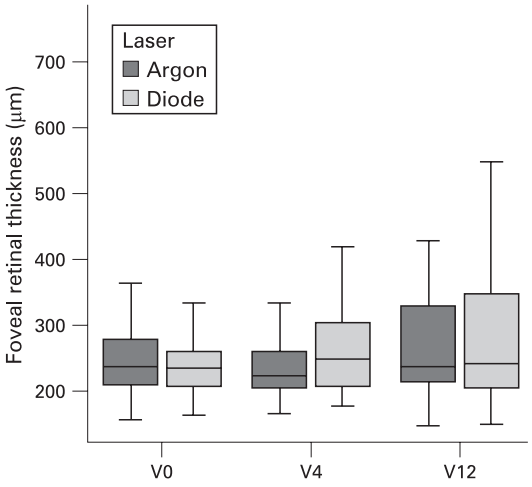

Figure 2 Boxplot (median and interquartile values) for central retinal thickness measured by the optical coherance tomography (OCT) at baseline (V0), 4 months (V4) and 12 months (V12). There was no statistical difference in the central macular thickness between the two groups of laser treatment at any time point.

Laser scars

Good quality fundus photos could be obtained only from 82 eyes at V12 (fig 3). The masked grader detected laser scars in six (13.9%) of the 43 eyes from MPDL group compared with 23 (59.0%) of the 39 eyes from CGL group. This difference was statistically significant (p = 0.001).

The risk of developing laser scars was 8.9 times higher in one eye treated with CGL than in one eye treated with MPDL (95% CI 3.0 to 26.0).

DISCUSSION

A series of case reports has suggested that sub-threshold micropulse laser photocoagulation is effective in the treatment of CSMO.[4–9] The only randomised controlled trial to date showed a very high re-treatment rate. We believe that the energy used in that study was too low.[10]

Although it is still controversial, the basis of the micropulse laser is that it allows some degree of heat dispersion during the treatment. This allows more energy to be applied to the retinal pigment epithelium with less collateral damage to the outer retina. More detailed descriptions of the micropulse have been published.[11 12] In brief, at 15% duty cycle, the laser is on for 300 ms and then off for 1700 ms at a 2 ms pulse. In a 300 ms treatment duration, 150 pulses are delivered.

The main problem with using the micropulse is that the treatment protocol is not well established. Based on the conditions used by Desmettre and colleagues, the micropulse energy at a 15% duty cycle is about four to six times the energy applied using a continuous wave.[11] Thus, in our protocol the energy used is about 30% of the equivalent of the continuous wave, as we doubled the power from the continuous wave. It is therefore significantly sub-threshold rather than just sub-threshold.

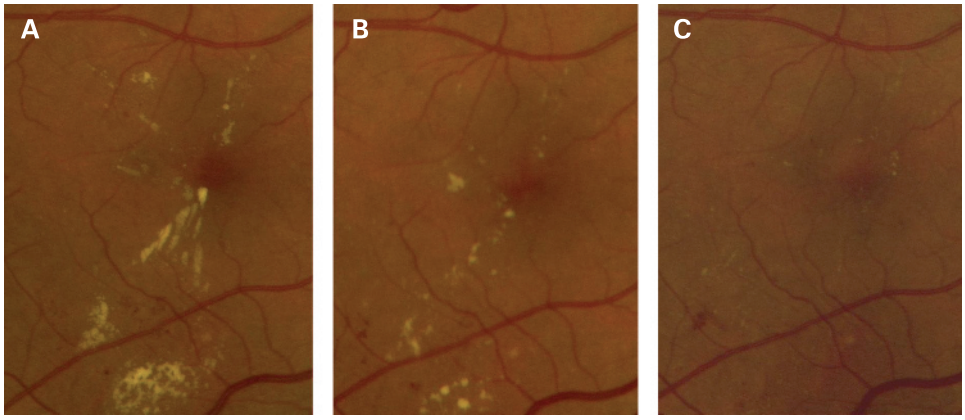

Figure 3 Fundus photographs at baseline (A), 4 months (B) and 12 months (C) showing the resolution of clinically significant macular oedema. Micropulse diode laser was applied at baseline.

The biological mechanisms involved in the resolution of diabetic macular oedema when treated by laser photocoagulation remain a matter of controversy. The similar results obtained with both MPDL and CGL suggest that the direct destruction of retinal tissue causing zones of retinal atrophy induced by CGL is not the major factor involved in the stabilisation process.[13 14] The energy delivered to the retinal pigment epithelium by the laser, which occurs in both types of treatment, appears to be more relevant.

It is possible that that turning the CGL power down would have the same effect as micropulsing. This will need to be examined in future randomised controlled trials, but it would not be ethically acceptable to compare two non-standard treatments.

We also noted less scarring in the MPDL group than in the CGL group. This is an important finding, as spread of retinal atrophy around conventional laser scars occurs over the years and is a frequent complication, particularly for macular laser.[15] It would be useful to observe whether these differences in retinal scarring are maintained in the long term.

CONCLUSION

The results of this prospective randomised double-masked study show that sub-threshold MPDL for diabetic CSMO compares well with CGL photocoagulation. Although the difference did not reach significant levels, it showed a trend for better vision at 12 months in the micropulse-treated eyes. There was no significant difference in contrast sensitivity and central retinal thickness between the two types of laser modality at 0, 4 and 12 months, suggesting similar efficacy.

The clinical significance of less visible scarring in the MPDL-treated eyes is yet to be determined. Theoretically, less scarring should result in better vision, but a longer follow-up period might be required to be able to demonstrate such a benefit.

Competing interests: None declared.

Ethics approval: The study was approved by Local Research Ethical Committee and Institutional Review Board at both centres.

Patient consent: Obtained.

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