Subthreshold 577 nm laser photocoagulation vesus conventional 532 nm laser photocoagulation for diabetic macular oedema

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Abstract

Purpose: To evaluate the visual and anatomic outcomes of the subthreshold micropulse 577 nm yellow diode laser (MYL) and to compare its efficacy with the conventional green 532 nm diode laser (CGL) in Asian eyes with diabetic macular oedema (DME).

Study design: Prospective randomized controlled clinical trial

Methods: Sixty-seven eyes of 43 patients with clinically significant macular oedema (CSME) were randomized to receive either MYL ($n = 37$) or CGL ($n = 30$) at baseline and were followed up for 12 months. Titration in the MYL group was performed with 15% duty cycle, 300 ms duration, and double the threshold power, while the modified Early Treatment of Diabetic Retinopathy Study (mETDRS) protocol was used for the CGL arm with the power titrated to a barely visible burn. Parameters noted included best-corrected visual acuity (BCVA) (logMAR), central subfoveal thickness (CST), macular volume (MV), and average macular thickness (AMT) using optical coherence tomography, and presence of visible laser scars on colour fundus photographs and fundus autofluorescence, at baseline and at 12 months.

Results: At 12 months follow-up, BCVA improved by 4.7 and 8.8 letters, respectively, for the MYL and CGL treatment arms ($p < 0.05$). There was a significant reduction in all retinal thickness parameters (CST, MV, and AMT) when compared to baseline

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in both laser treatment arms at 12 months. There was no significant difference in either BCVA or retinal thickness parameters between the two treatment arms at 1, 3, 6, 9, or 12-month follow-up. Laser scars were observed in 26.7% of patients in the MYL group compared to 75% of patients in the CGL group (p = 0.029).

Conclusions: MYL is an effective, safe, and patient-friendly treatment option for clinically significant macular oedema, with improvement in BCVA, reduction in macular thickness, and less scarring after treatment at 12 months.

Keywords: clinically significant macular oedema, diabetic macular oedema, sub-threshold laser photocoagulation, subthreshold yellow laser

Abstrak

Tujuan: Untuk membandingkan keberkesanan di antara mikropulse subthreshold 577 nm laser diod kuning (MYL) dan laser diod 532 nm (CGL) konvensional pada pesakit diabetis berasal dari Asia yang mengalami edema macular ("diabetic macular edema" [DME]) dari segi penglihatan dan anatomi makular.

Reka bentuk kajian: Kajian klinikal terkawal prospektif secara rawak

Kaedah kajian: Kajian ini melibatkan 67 mata dari 43 pesakit diabetis dengan edema makula yang signifikan secara klinikal ("clinical significant macular edema" [CSME]) secara rawak untuk menerima rawatan laser samada MYL (n = 37) atau CGL (n = 30) pada permulaan rawatan dan disusulkan selama 12 bulan. Dalam kumpualan MYL, titrasi dilakukan dengan 15% kitaran selama 300 ms dan menggandakan daya ambang. Sementara rawatan modifikasi protokol "Early Treatment of Diabetic Retinopathy Study" (mETDRS) digunakan bagi kumpulan CGL dengan dititrasikan dengan kesan parut pembakaran laser yang hampir tidak kelihatan pada makular. Ketajaman penglihatan yang terbaik setelah diperbetulkan ("best corrected visual acuity" [BCVA]) menggunakan unit logaritma sudut resolusi minimum (logMAR) dan parameter anatomi termasuk ketebalan subfoveal tengah (CST), isipadu makular (MV) dan purata ketebalan makula (AMT) menggunakan tomografi koheren optikal (OCT) , beserta kesan parut pembakaran laser pada retina yang dikesan melalui foto dan autofluoresensi pada foto fundus. Semua parameter ini didokumentasikan pada peringkat permulaan rawatan dan setelah 12 bulan selepas rawatn.

Keputusan: Pada 12 bulan susulan selepas rawatan, BCVA meningkat sebanyak 4.7 huruf bagi kumpulan MYL dan 8.8 huruf untuk kumpulan CGL (p < 0,05). Terdapat penurunan yang signifikan dalam semua parameter ketebalan retina (CST, MV, dan AMT) berbanding bacaan pada permulaan rawatan bagi kedua-dua kumpulan. Tetapi tiada perbezaan yang signifikan dari segi ketajaman penglihatan BCVA mahupun parameter melibatkan ketebalan retina pada 1, 3, 6, 9 atau 12 bulan susulan di antara kedua-dua kumpulan. Kesan laser dapat dilihat pada 26.7% pesakit

dalam kumpulan MYL berbanding 75% pesakit dalam kumpulan CGL (p = 0.029). *Kesimpulan:* MYL adalah efektif untuk rawatan CSME dari segi peningkatan BCVA dan mengurangkan ketebalan macula secara anatomi, mengurangkan kesan parut dan mesra pesakit selepas rawatan pada 12 bulan.

Kata kekunci: clinically significant macular oedema, diabetic macular oedema, subthreshold laser photocoagulation, subthreshold yellow laser

Introduction

Diabetic macular oedema (DME) is the most common cause of moderate visual loss in the working-age population in patients with diabetes mellitus (DM), with a 10-year cumulative incidence of 20.1% and 25.4% for patients with type 1 and 2 DM, respectively.[1,2] The landmark Early Treatment of Diabetic Retinopathy Study (ETDRS) showed that argon laser photocoagulation decreases the risk of moderate visual loss in clinically significant macular oedema (CSME) by 50% and was the mainstay of treatment for many years.[3,4] However, the conventional laser uses continuous-wave energy that produces a visible burn on the retina and has several complications such as scotomas, visual field defects, chorioretinal atrophy, macular creep, choroidal neovascularization, and subretinal fibrosis.[5-7]

To address these risks and to reduce potential collateral damage, the subthreshold diode laser was introduced. In 1997, Friberg and Karatza first reported the clinical application of subthreshold micropulse 810 nm diode laser treatment in DME[8] and several studies have demonstrated its efficacy in different macular diseases.[9-14] Subthreshold micropulse laser treatment uses a shorter exposure time and a subvisible clinical endpoint (in which no coagulation spot is observed), delivering laser energy by dividing the beam into a series of short laser pulses (100–300 µs). Every single pulse has an on and off duration (duty cycle), enabling tissues to cool down to baseline temperature before the next pulse.[15] By using a low laser power, it avoids protein coagulation and targets almost selectively the melanocytes within the retinal pigment epithelium (RPE), with minimum damage to the neural retina and choroidal layers.[16]

The beneficial effect of a subthreshold laser works by reducing Müller cell activation, as well as decreasing production of cytokines and vasoactive substances, thus leading to less capillary permeability, suppression of vascular endothelial growth factor (VEGF), and upregulation of pigment epithelium-derived factor (PEDF), and improving retinal function, stabilizing visual acuity, and decreasing macular oedema.[17-20]

The subthreshold micropulse diode laser is available in different wavelengths: 532 nm, 577 nm, or 810 nm. Theoretically, yellow (577 nm) wavelength diode lasers offer some advantages for macular tissues as they are not absorbed by the

xanthophyll pigment in the macula, thereby allowing retreatment sessions and application directly to the centre of the fovea.[13,20] It is better absorbed by RPE melanin and haemoglobin compared to the 810 nm infrared laser wavelength and causes less scatter compared to 532 nm, thereby allowing use of lower powers and shorter pulse durations.[20]

We conducted a prospective, randomized controlled clinical trial to evaluate the visual and anatomic outcomes of the subthreshold 577 nm yellow diode laser (MYL) and compare its efficacy with the conventional green 532 nm diode laser (CGL) in Asian eyes with DME.

Methods

Study design

This study was a prospective, randomized, controlled clinical trial performed at the Eye Clinic of University of Malaya Medical Centre (UMMC) from August 2009 to December 2011. The study was approved by the UMMC Ethics Committee and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients who participated in the study. This study was listed on www.clinicaltrials.gov, under identifier NCT01045239.

Patient selection

Patients with type 2 DM with DME were enrolled from the Eye Clinic of UMMC in a consecutive if eligible basis. Eligibility criteria included diagnosis of CSME using the ETDRS criteria[3] on biomicroscopy and best-corrected visual acuity (BCVA) between 15 and 68 letters on the modified ETDRS chart (logMAR 1.0).

The exclusion criteria included macular oedema caused by a disease other than diabetes; pre-existing ocular conditions that can interfere with visual acuity improvement (foveal atrophy, pigment abnormalities, dense subfoveal hard exudates, significant macular ischemia, vein occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma, etc.); dense media opacity; history of treatment for DME at any time in the previous 4 months (such as focal/grid macular photocoagulation, intravitreal or peribulbar corticosteroids, anti-VEGF drugs); history of panretinal photocoagulation (PRP) within 4 months prior to enrolment or anticipated to be performed within the next 6 months, and history of major ocular surgery (including vitrectomy, cataract extraction, scleral buckle, or any intraocular surgery, etc.) within the previous 4 months or anticipated within the next 6 months.

Patients were randomly assigned to receive treatment with MYL or CGL using sequentially numbered, opaque sealed envelopes (SNOSE). At the initial visit, a detailed history was recorded for all patients including duration of DM, past glycaemic control (HbA$_1$c), medications, and general medical and ocular history. All patients were examined at baseline and at 1, 3, 6, 9, and 12 months after treatment.

At each visit, patients underwent BCVA measurement, slit lamp biomicroscopy, fundus photography, and macular thickness measured by spectral-domain optical coherence tomography (SD-OCT) (Cirrus HD OCT version 5.0, Carl Zeiss Meditec, Dublin, USA). For SD-OCT measurement, three parameters were recorded: central subfoveal thickness (CST), macular volume (MV), and average macular thickness (AMT). Fundus fluorescein angiography (FFA) was done if deemed necessary by the assessing ophthalmologist to assess macular ischaemia or leakage. Fundus colour photographs and fundus autofluorescence (FAF) imaging were performed on all patients. The images taken at baseline and at 12 months follow-up were graded by an independent centre, the Singapore Advanced Imaging Laboratory for Ocular Research (SAILOR), Singapore Eye Research Institute, in order to identify new laser scars. During follow-up, the patients were assessed by an independent data collector for visual acuity, SD-OCT measurements, and fundus photos. Clinical assessment, including noting of macular scars on slit lamp biomicroscopy was done by another investigator who was blinded to the treatment patients had received. The treating ophthalmologists were not involved in follow-up assessments of the patients.

Treatment technique
CGL was performed with a 532 nm diode green laser light using the Zeiss Visulas diode laser (Carl Zeiss Meditec, Jena, Germany). We followed the modified-ETDRS technique of 100 µm spot sizes with an exposure time of 100 ms. The power was adjusted by slowly increasing the laser power until a light grey-white (just visible) burn was obtained.[21] Treatment was performed up to 500 µm from the centre of the foveal avascular zone.

MYL was performed using laser light at 577 nm using a Quantel Supra 577 diode laser (Quantel Medical, Cedex, France). The subthreshold laser power was derived from a test burn. The test burn was performed in the continuous wave mode using a 100 µm spot diameter and a 300 ms duration in the nasal side outside the vascular arcade with the power titrated until a burn became barely visible.[11] The diode laser was switched from continuous wave emission mode to subthreshold emission mode at 15% duty cycles, 300 ms duration, and the power to achieve the visible laser burn doubled. Treatment was applied in a confluent fashion to the entire area of macular oedema without any visible burns on the retina.

If there was little or no improvement of the condition, laser treatment was repeated at 16 weeks intervals, with a maximum of three treatment sessions. Patients with recalcitrant macular oedema were offered other treatment options after the maximum three laser sessions.

Statistical analysis
The paired t-test was used to test for significant mean deviation of the four parameters: BCVA, CST, AMT, and MV at five time periods (1, 3, 6, 9 and 12 months

after treatment) against the baseline within the CGL and MYL treatment arms. To test whether the mean deviation in the CGL treatment arm differed significantly from that of the MYL treatment arm, the two-sample t-test was used. Bonferroni adjustment to the significance level of 5% was done in the five comparisons, resulting in actual significance level of 1.7% per test.

Patients within each laser treatment group were further stratified into two groups based on:
    i.   CST levels at baseline (400 µm or higher; below 400 µm)
    ii. oedema type (focal or diffuse).
Focal oedema was defined as having fewer than four parafoveal OCT quadrants greater than 300 µm and diffuse oedema was defined as having all four parafoveal quadrants greater than 300 µm in thickness.[19]

Two-factor ANOVA was used to check for interaction between laser treatment and the stratifying variable. This was followed by two-sample t-tests (for six time points) between the levels of the stratifying variable within a particular laser treatment arm, and then between laser treatments within a particular level of the stratifying variable. As six separate tests were done, Bonferroni adjustment to the significance level of 5% resulted in actual significance level of 0.8% per test.

The presence of visible macular scars at 12 months was also compared to baseline. Chi-square test (Pearson chi-square) was used to assessed statistical difference. A p-value < 0.05 was considered to be significant. The statistical analyses were carried out using R version 2.13.1 (R Development Core Team, 2011).

Table 1. Clinical characteristics of patients at baseline in the green and yellow laser treatment arms

Characteristics	MYL (n = 37) Mean (SD)	CGL (n = 30) Mean (SD)	p
Age (years)	59.4 (7.5)	61.1 (7.6)	0.677
Diabetic duration (years)	15.0 (7.0)	12.7 (5.8)	0.142
HbA1c (%)	8.6 (1.7)	8.9 (1.7)	0.654
Diastolic blood pressure (mmHg)	78.6 (11.2)	78.3 (11.3)	0.905
Systolic blood pressure (mmHg)	143.2 (18.0)	144.1 (28.6)	0.866
BCVA (letters)	36.3 (12.1)	34.5 (14.6)	0.548

Values shown are mean values. The standard deviation (SD) is stated in parentheses.
BCVA: best-corrected visual acuity; MYL: micropulse yellow laser; CGL: conventional green laser

Table 2. Classification of oedema and number of laser treatment for eyes in the CGL and MYL treatment groups

	Type of Oedema						Number of laser treatments			
	Diffuse *n* (%)	Focal *n* (%)	Total *n* (%)	CST < 400 µm *n* (%)	CST ≥ 400 µm *n* (%)	Total	1	2	3	Total (Average)
CGL	17 (57%)	13 (43%)	30	23 (77%)	7 (23%)	30	9	18	3	30 (1.8)
MYL	28 (76%)	9 (24%)	37	24 (65%)	13 (35%)	37	12	17	8	37 (1.9)

MYL: micropulse yellow laser; CGL: conventional green laser; CST: central subfoveal thickness

Results

Sixty-seven eyes of 43 patients (20 men and 23 women) completed follow-up at 12 months. Thirty-seven eyes received MYL and 30 eyes received CGL. The mean age was 60.25 ± 7.5 years. The mean duration of DM was 14.3 ± 6.52 years and the mean HbA1c at baseline visit was 8.7 ± 1.6%. There were no significant differences in parameters between the two laser arms at the baseline visit (Table 1).

In the subgroup analysis, 23% of patients in the CGL arm and 35% of patients in the MYL arm had a baseline CST of > 400 µm (Table 2). There were 76% of patients with diffuse oedema in the MYL arm compared with 57% in the CGL arm.

Visual acuity
At baseline, mean BCVA was 36.3 (standard deviation, SD 12.1) in the MYL arm and 34.5 (SD 14.6) in the CGL arm. Eyes in both treatment arms showed statistically significant improvement in mean BCVA 12 months after treatment, with a gain of 4.7 letters in the MYL group [95% confidence interval (CI): 0.9, 8.4; $p < 0.01$] and 8.8 (95% CI: 3.9, 13.7; $p < 0.01$] letters in the CGL group (Fig. 1). However, there was no statistical difference in mean BCVA from baseline to 12 months between both treatment arms, $p = 0.44$.

Macular thickness
Mean CST at baseline was 353.64 µm in the MYL arm and 351.38 µm in the CGL arm. At 12 months follow-up, the mean reduction in CST was 65.7 µm in the MYL arm (95% CI: -104.5, -27; $p < 0.01$) and 58.5 µm in the CGL arm (95% CI: -107.8, -9.2; $p < 0.01$) (Fig. 2).
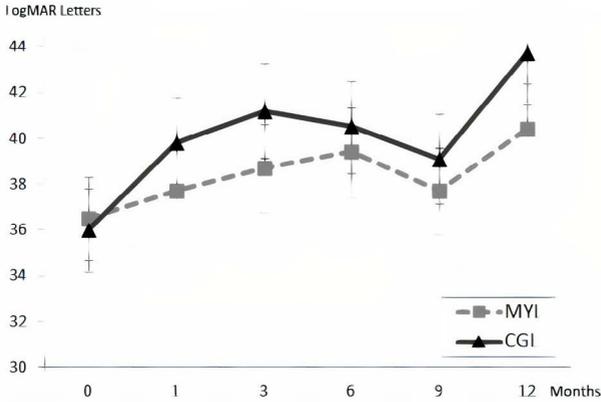
Fig. 1. Visual acuity of patients in the micropulse yellow laser (MYL) and conventional green laser (CGL) treatment groups at baseline and 1, 3, 6, 9, and 12 months after treatment.
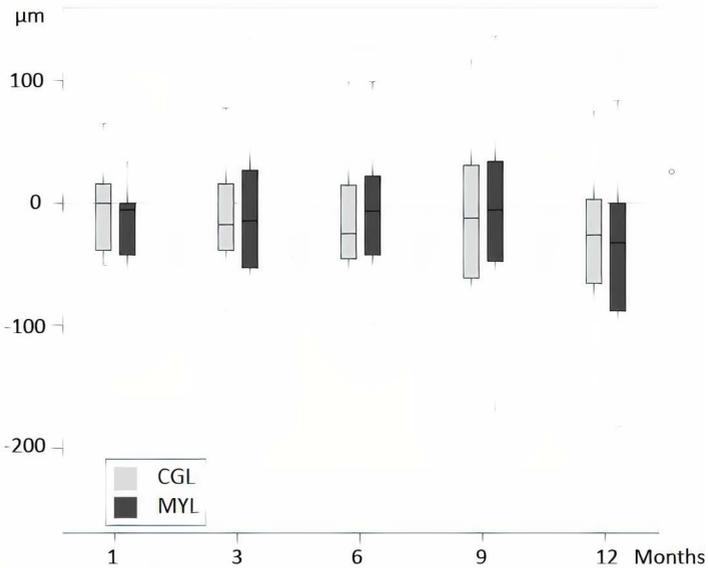

Fig. 2. Changes in central subfield thickness of patients in the micropulse yellow laser (MYL) and conventional green laser (CGL) treatment groups at baseline and 1, 3, 6, 9, and 12 months after treatment.

There was no statistical difference in the reduction in CST from baseline to 12 months between both treatment arms ($p = 0.67$).

Mean MV at baseline was 11.37 mm^3 in the MYL arm and 10.60 mm^3 in the CGL arm. Mean reduction in MV at 12 months was 0.88 mm^3 in the MYL arm (95% CI: -1.3, -0.3; $p < 0.01$) and 0.69 mm^3 in the CGL arm (95% CI: -1.0, -0.2; $p < 0.01$), with no significant difference between both treatment arms ($p = 0.43$).

Mean AMT at baseline was 315.81 μm in the MYL arm and 300.63 μm in the CGL arm. At 12 months follow-up, the mean reduction in AMT was 24.4 μm in the MYL group (95% CI: -39.5, -9.4; $p < 0.01$) and 16.1 μm in the CGL group (95% CI: -28.2, -4.1; $p < 0.01$), with no significant difference between both arms ($p = 0.88$).

Subgroup analysis

For the subgroup analysis of CST ≥ 400 μm and < 400 μm, there was no statistically significant difference in BCVA in both the CGL and MYL arms at 12 months follow-up. However, the CST ≥ 400 μm subgroup showed significant reduction in thickness

Table 3. Difference in mean improvement in BCVA and CST at 12 months compared to baseline between the subgroups with baseline CST < 400 μm and ≥ 400 μm

	Yellow			Green		
	Baseline CST < 400 μm Mean (SD)	Baseline CST ≥ 400 μm Mean (SD)	p	Baseline CST < 400 μm Mean (SD)	Baseline CST ≥ 400 μm Mean (SD)	p
BCVA	3.1 (10.6)	4.2 (8.5)	0.99	7.4 (7.5)	9.3 (12.5)	0.83
CST	8.9 (64.5)	117.6 (90.0)	0.01	21.4 (42.5)	130.7 (117.1)	**0.03**

BCVA: best-corrected visual acuity; CST: central subfoveal thickness

Table 4. Difference in mean improvement in BCVA and CST at 12 months compared to baseline between the focal and diffuse subgroups

	Yellow			Green		
	Focal Mean (SD)	Diffuse Mean (SD)	p	Focal Mean (SD)	Diffuse Mean (SD)	p
BCVA	3.3 (5.8)	5.4 (8.3)	0.19	8.0 (9.4)	9.25 (9.0)	0.47
CST	25.1 (42.7)	62.1 (88.0)	0.58	35.2 (46.7)	60.3 (101.1)	0.50

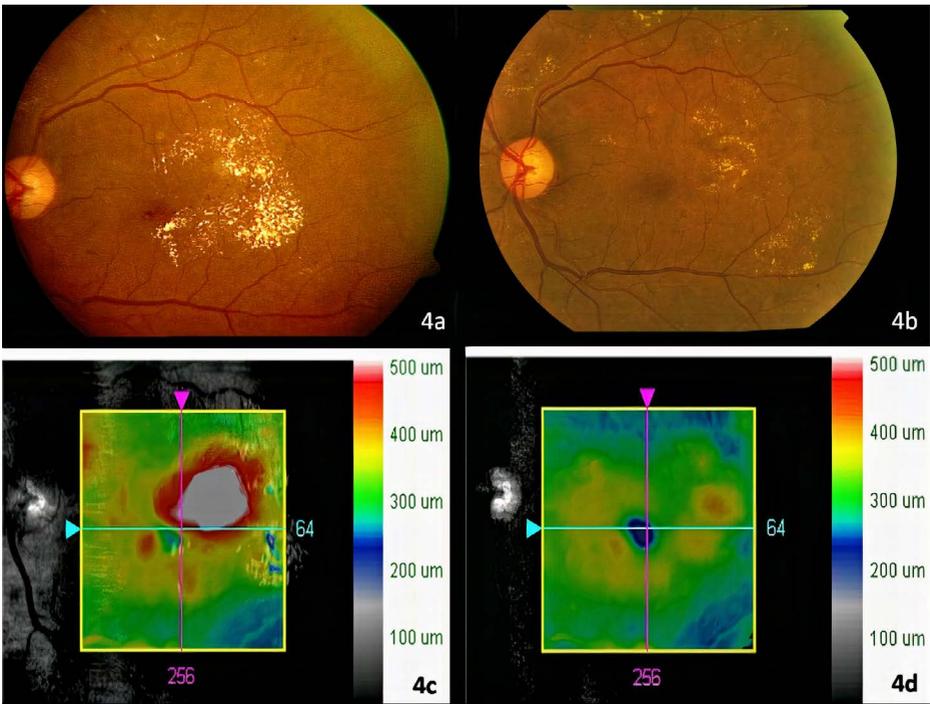BCVA: best-corrected visual acuity; CST: central subfoveal thickness

Fig. 3. Composite image showing colour fundus photographs of the macula and SD-OCT images at baseline and 12 months after treatment with micropulse yellow laser. The oedema resolved and visual acuity improved from 37 letters to 57 letters. No laser scars were seen at the macula.

compared to the CST < 400 μm subgroup in both treatment arms (Table 3). There was no significant difference in BCVA or improvement in CST between the focal and diffuse DME groups in both the CGL and MYL arms at 12 months follow-up (Table 4).

Laser scars
Seventy-five percent of eyes in the CGL arm showed visible scarring on slit lamp bio-microscopy and/or fundus photographs at 12 months follow-up compared to only 26.7% in the MYL arm, $p < 0.001$. FAF of the laser scars, either decreased or increased FAF, were detected in 88.9% and 41.7% of eyes in the CGL and MYL laser groups, respectively, $p = 0.003$. Figures 3 and 4 are composite images showing colour fundus photographs of the macula and SD-OCT images at baseline and 12 months after treatment with MYL and CGL, respectively.
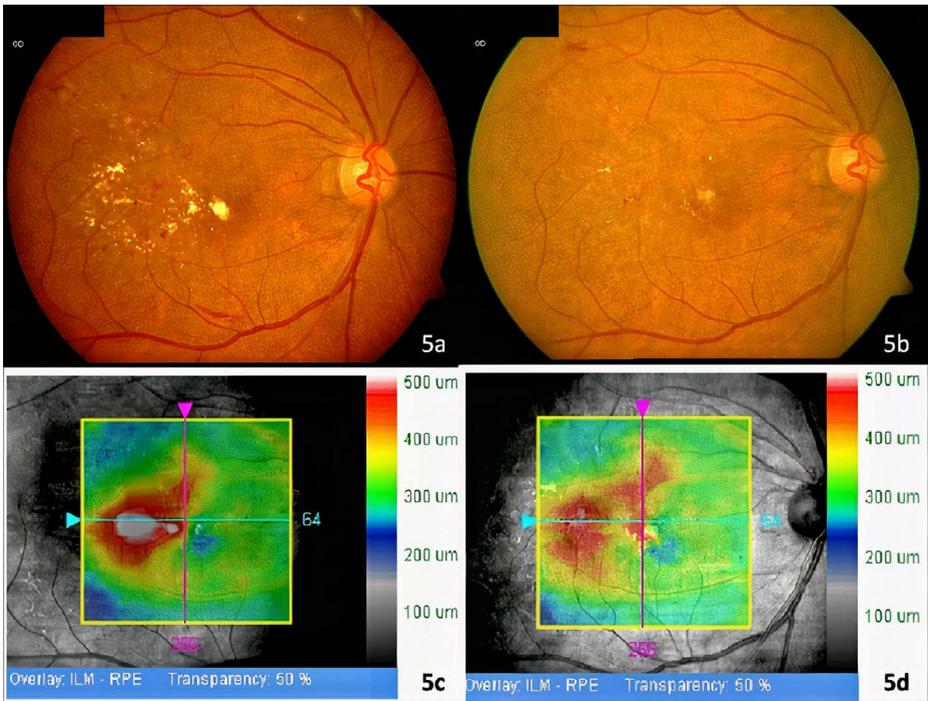
Fig. 4. Composite image showing colour fundus photographs of the macula and SD-OCT images at baseline and 12 months after treatment with conventional green laser. Note the presence of laser scars temporal to the macula.

Discussion

The World Health Organization has estimated Malaysia will have a total of 2.48 million people with DM by 2030.[22] The Singapore Malay Eye Study on 3,280 Malay adults 40 to 80 years with DM revealed a 35.0% prevalence of any form of diabetic retinopathy; 4.9% with proliferative DR and 35.0% with macular oedema.[23] Intravitreal anti-VEGF and steroids are the current treatment of choice in management of DME.[24-26] Nevertheless, intravitreal anti-VEGFs require repeated injections and frequent visits to maintain the visual and anatomic gains, causing a huge economic burden. Also, DME is sometimes resistant to these therapies and may require other treatment modalities.[27]

Subthreshold laser is a novel, tissue-sparing approach to treat DME that preserves macular function and causes less iatrogenic damage to the tissues surrounding the area of the burn in the RPE. While most of the initial studies on subthreshold laser used the 810 nm infrared laser, some studies have explored the use of 532 nm green

and 577 nm yellow lasers for the treatment of DME. In this randomized controlled trial, we showed that the subthreshold 577 nm yellow laser was as effective as conventional modified-ETDRS green laser photocoagulation in the treatment of DME, with a much lower incidence of scarring at 12 months.

We found significant improvement in BCVA in both treatment arms at 12 months, (8.8 letters in the CGL arm *versus* 4.7 letters in the MYL arm improvement; p = 0.44). All 3 SD-OCT parameters (CST, MV, and AMT) measured showed a statistically significant reduction in macular oedema for both treatment arms. Previous studies have reported the excellent effect of subthreshold diode laser treatment on DME in terms of improved visual acuity and decreased thickness on OCT without any structural damage in the retinal layers.[14, 28-30,] Pei-Pei *et al.* found that green 532 nm PASCAL subthreshold laser was equally effective in improvement of mean BCVA and CMT as threshold laser grid treatment for patients with DME.[31] Vujosevic *et al.* found no differences in CMT, MV, foveal choroidal thickness, and BCVA between the yellow and infrared subthreshold laser in mild, centre-involving DME with the lowest duty cycle (5%) and fixed power parameters.[32] Luttrull and Sinclair addressed the issue of the ability to treat the fovea directly with a transfoveal subthreshold infrared laser in cases of centre-involving DME and found it to be safe and effective with no evidence of laser-induced macular damage by any imaging means postoperatively and no adverse treatment effects.[13]

In our subgroup analysis, patients with ≥ 400 μm CST at baseline had significantly more reduction in CST at 12 months compared to those patients with baseline CST < 400 μm in both treatment arms. However, this difference was not reflected in the BCVA, with no significant difference seen between both subgroups at 12 months in both treatment arms (p = 0.83). Anatomical improvement is not always associated with improvement in functional outcomes.[33-36] Studies by the Diabetic Retinopathy Clinical Research network found only a modest correlation between the change in central foveal point thickness and that in BCVA (r = 0.44).[34,35] Soliman *et al.* found that eyes in which more retinal layers were involved at baseline had a poorer functional outcome than eyes in which fewer layers were involved.[37] Mansouri *et al.* reported that subthreshold diode macular laser may be more effective in subjects with mild to moderate DME, as subjects with initial CST ≤ 400 μm responded better in terms of visual acuity gain and decrease in foveal thickness compared to those with central foveal thickness > 400 μm.[38] Valera-Cornejo *et al.* found more improvement in central macular thickness (CMT) in subjects with treatment-naïve, centre-involving DME at 3 months compared to those with refractory DME using yellow 577 nm subthreshold laser photocoagulation (p = 0.011).[39] A thicker retina at baseline is reflective of more severe and/or longer-standing disease. The exact cause of this lack of response to subthreshold laser in patients with severe anatomical disease is not clear. Mansouri *et al.* hypothesized that the concentration of cytokines released by the laser stimulation of RPE in severe oedema may be diluted or there might be alterations in distribution of laser energy throughout the retina and RPE due to intra-

and subretinal fluids present in these cases.[38] Perhaps different laser parameters are required in patients with greater oedema. All these studies reiterate that an anatomical reduction of macular oedema is not always followed by an improvement in visual acuity, and the relationship between these two variables is weak.

Another option might be to reduce the macular oedema with anti-VEGF agents or steroids prior to the application of subthreshold laser. Akhalagi showed that using subthreshold diode laser in combination with intravitreal *bevacizumab* can significantly reduce CMT and improve visual acuity in patients with refractory DME.[40] Moisseiev *et al.* reported that subjects treated with a combined therapy of anti-VEGF (ranibizumab) and subthreshold laser needed significantly fewer injections than those treated with ranibizumab alone (2.6 *versus* 9.3 at the end of the follow-up).[41]

In our study, we noted that the patients in the MYL arm had significantly less scarring on slit lamp biomicroscopy (75% *versus* 26.7%) and on FAF (88.9 % *versus* 41.7 %) compared to those in the CGL arm. This is comparable to the findings of Figuera *et al.*, who found a difference of 45% between the two laser treatment modalities.[10] In contrast to this, Luttrull *et al.* found that the incidence of FAF changes in subthreshold 810 nm diode laser ranged from 0% to 8% only, depending on the duty cycle used.[12] Luttrull *et al.* used high-density/low-intensity parameters with a large number of small, densely placed, short-duration laser spots (high density) at a 5% duty cycle (low intensity) to maximize heat dissipation and minimize heat accumulation, thereby reducing the risk of unintended thermal retinal injury.[12] They noted that subthreshold laser at higher retinal irradiance levels (by decreasing wavelength or increasing duty cycle more than 5%) appeared to significantly increase the risk of thermal retinal injury, especially in more darkly pigmented eyes. This could have been the reason for scarring seen in some cases in our MYL arm. Vujosevic *et al.* found no changes indicating damage to the RPE on FAF after subthreshold laser treatment for DME in a prospective study on 50 patients (125-mm spot size, 5% duty cycle of 0.2 seconds, 750 mW power).[11] Lavinsky *et al.* did a detailed analysis of retinal structures changes under certain fluence reductions and concluded that 30% of threshold energy does not create any tissue defects.[42] Chhablani *et al.* reported that the 15% duty cycle setting seems to achieve the highest ETDRS letter gain and largest decrease in volume compared to the 5% duty cycle parameters using 577 nm subthreshold laser with power reduced to 30% of continuous wave laser.[43] Our study was performed in 2011–2012, before the publication of these studies. We followed an earlier protocol used by Figuera *et al.*[10] for the subthreshold laser, with 300 ms and double the power used for the test burn. With the benefit of hindsight, reducing the exposure to 100 ms and careful power titration with 15 % duty cycle to achieve 30% of threshold energy would probably have reduced the scarring even further. The main challenge faced by ophthalmologists while using the subthreshold laser is difficulty in titration and documentation of treatment, as there is no actual endpoint, such as a visible burn. Subthreshold laser parameters and titration protocols vary significantly between studies and there is no strong recommenda-

Table 5. Protocols used for subthreshold micropulse laser in different studies for diabetic macular oedema

Author (Year)	Spot size (μm)	Duty cycle (%)	Duration of exposure (ms)	Power
Lutrull *et al.* (2005)[9]	125	5	300	Fixed at 750mW
Figuera *et al.* (2009)[10]	125	15	300	CWL power doubled
Vujosevic *et al.* (2010)[11]	125	5	200	750mW (fixed) with infrared laser
Lavinsky *et al.* (2011)[14]	125	15	300	CWL power increased by 20%
Lutrull *et al.* (2014)[13] 2 protocols	125 125	5 5	300 300	Fixed power of 950mW Fixed power of 780mW
Mansouri *et al.* (2014)[38]	125	5	300	Fixed power of 950 mW
Vujosevic *et al.* (2015)[32] 2 protocols	100 125	5 5	200 200	250mW with yellow laser (fixed) 750 Mw with infrared laser (fixed)
Chhablani *et al.* (2018)[43] 2 protocols	100 100	5 15	100 100	Power titrated to 30% of CWL
Akhlaghi *et al.* (2019)[40]	200	5	NA	Titrated to four times the CWL power
Bougatsou *et al.* (2020)[28]	100	15	100	Titrated to double the CWL power
Valera-Cornejo *et al.* (2021)[39]	100–150	5	200	Power reduced to 50% of CWL

CWL: continuous-wave laser

tion so far about ideal parameters for DME treatment. Some authors advocate fixed parameters while others prefer varied methods of titration. The different protocols used in various studies are listed in Table 5.

The strengths of this study are it is a single-centre, prospective, randomized, and controlled nature standardized measurements and laser protocol, and adequate follow-up period of 12 months. All the patients were treated by only two ophthalmologists so as to reduce the bias in difference in technique. The weaknesses of this study were its small sample size and lack of functional visual assessment such as

microperimetry and contrast sensitivity. The patients in our study had poor diabetic control, which also makes the management of DME harder. However, this situation reflects the real-life challenging scenario faced by many ophthalmologists treating DME.

Conclusion

In conclusion, our results revealed that MYL is an effective, safe, and patient-friendly treatment option for CSME, with improvement in BCVA, reduction in macular thickness, and less scarring after treatment at 12 months.

Declarations

Ethics approval and consent to participate
This study was a prospective, randomized, controlled clinical trial performed at the Eye Clinic of University of Malaya Medical Centre (UMMC) from August 2009 to December 2011. The study was approved by the UMMC Ethics Committee and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients who participated in the study. This study was listed on www.clinicaltrials.gov, under identifier NCT01045239.

Competing interests
The authors declare they have no competing interests.

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