Comparison of Subthreshold 532 nm Diode Micropulse Laser with Conventional Laser Photocoagulation in the Treatment of Non-Centre Involved Clinically Significant Diabetic Macular Edema

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ABSTRACT

Background: The aim of the study was to investigate the effect of the 532 nm (green) diode subthreshold micropulse laser (SML) in the treatment of non-centre involved clinically significant macular edema (CSME) in comparison to the conventional laser photocoagulation (CLP).

Methods: A total of 60 eyes of patients diagnosed with non-centre involved CSME were randomly divided into two groups. SML photocoagulation was performed in the first group (G1), while CLP in the second one (G2). Central macular thickness (CMT) and best corrected visual acuity (BCVA) were measured prior to treatment and at 3 and 6 months after intervention.

Results: G1 participants had significantly better CMT at 6 months after laser application ($p = 0.04$) compared to G2. Additionally, CMT in both groups was significantly lower 6 months after laser application in comparison to baseline values (G1: $p < 0.001$, G2: $p = 0.002$). Moreover, significant improvement was detected 6 months after SML in G1 regarding BCVA compared to values before laser treatment ($p = 0.001$).

Conclusion: SML was more effective than CLP in reducing CMT and improving BCVA in patients with non-centre involved CSME. Therefore, it seems that SML can be a good substitute for CLP in DME treatment if confirmed in future studies.

KEYWORDS

micropulse laser; subthreshold laser; 532 nm; conventional laser photocoagulation; diabetic macular edema

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INTRODUCTION

Diabetic retinopathy (DR), the most common and severe ocular complication of diabetes mellitus (DM), remains the leading cause of preventable blindness in the working-age population in developed countries (1–3). Diabetic Macular Edema (DME), a frequent complication of DR, constitutes one of the main causes of visual impairment in DR patients (4–6). It is defined by the presence of retinal edema involving or threatening the fovea in patients with DM (7). According to epidemiologic studies, it is estimated that approximately one third of patients with DM have signs of DR, and one third of them suffer from vision threatening DR, including DME (8). The most severe spectrum of DME is clinically significant macular edema (CSME), which is defined as 1) retinal thickening (edema) at or within 500 μm of the center of the fovea or 2) hard exudates at or within 500 μm of the foveal center if associated with thickening of the adjacent retina and/or 3) zones of retinal thickening 1 disc area in size, at least part of which being within 1 disc diameter of the center (8).

Since the early treatment diabetic retinopathy study (ETDRS) (9, 10) showed that laser photocoagulation reduces the risk of visual acuity decrease by 50% in eyes with CSME, continuous-wave laser photocoagulation has been the standard treatment of DME for many years. Depending on the type of edema, conventional laser photocoagulation (CLP) pattern varies: focal photocoagulation is used for localized leakage areas and microaneurysms in focal DME, while grid pattern for diffuse edema (7). However, these methods have numerous disadvantages; among them deterioration of contrast sensitivity, of colour vision and of visual field (11) as well as potential complications, such as epiretinal fibrosis, subretinal scarring, choroidal neovascularization (CNV) and progressive enlargement of laser scars leading to foveal atrophy (12–14). These side effects have been associated with the spread of thermal energy from the single laser burns which contribute to collateral damage to the neighboring sensory retina and the choroid when continuous-wave mode is used (15).

To address potential collateral damage, micropulse lasers have been introduced. These lasers allow the management of DME. No scar or burn can be visualized with the subthreshold micropulse laser (SML) treatment (15). The subthreshold micropulse diode laser is available in different wavelenghts: 532 nm, 577 nm, or 810 nm. With micropulse mode, the laser energy is delivered in many repetitive short impulses [measured in microseconds (μs) – "micropulses"], within an "ON" cycle and an "OFF" cycle. The "ON" time, which is the duration of each micropulse, typically has a length of 100 to 300 μs, and the "OFF" time, which is the time between the pulses, has a duration of 1700 to 1900 μs (15).

The longer "OFF" interval plays a significant role in the protection of the overlying neural retina because it enables the tissues to "cool down". As a result, the diffusion of heat into the surrounding tissues is minimized and thus scarring is avoided. Former histological reports confirmed that the energy of SML affects almost selectively the melanocytes within the retinal pigment epithelium (PRE) with a minimum damage to the neural retina and choroidal layers (16). Laser power is set at a low level, so that the laser impact does not leave any visible lesion on the retina. In consequence, only a limited thermal impact is applied on the tissue, without exceeding the protein denaturation threshold of neural retina and without having any lethal effect (17). According to recent studies, still-viable RPE cells surrounding the burned areas appear a healing response to thermal injury by activating a therapeutic cellular cascade (18). In this way, vascular endothelial growth factor (VEGF) and neovascularization is suppressed, pigment epithelium-derived factor (PEDF) is up-regulated, the expression of other cytokines is modified, as well (19), resulting in the improvement of the retinal function, stabilizing visual acuity and decreasing macular edema (18, 20).

Therefore, the SML application can reduce the aforementioned complications induced by the laser heat associated with continuous-wave CLP and can lead to less negative impact on visual function. However, taking into account that SML uses smaller amount of energy per treatment, it may be possible that micropulse mode may not be as effective as continuous-wave CLP mode in the reduction of DME and therefore in the decrease of central macular thickness (CMT) (15).

To the best of our knowledge, there has been no clinical trial comparing the outcomes of 532 nm SML versus CLP in patients with non-centre involved CSME. Within this context, primary objective of this study was to investigate the efficacy of SML in the treatment of the non-centre involved CSME.

MATERIAL AND METHODS

SETTING

This is a prospective, comparative, randomized trial. Study protocol adhered to the tenets of the Declaration of Helsinki and written informed consent was provided by all participants. The institutional review board of Democritus University of Thrace approved the study protocol. The study was conducted at the Department of Ophthalmology in the University Hospital of Alexandroupolis, Greece, between January 2017 and June 2017.

PARTICIPANTS

Participants were enrolled from the Medical Retina Service of the hospital in a consecutive-if-eligible basis. Eligibility criteria included diagnosis of non-centre involved CSME. Patients populated randomly two distinct groups for the purposes of this study: 1) G1 group: patients that underwent SML, 2) G2 group: patients that underwent conventional focal laser photocoagulation. Exclusion criteria for all study groups included: 1) Former laser application and intravitreal anti-VEGF therapy, 2) eye conditions or other co-morbidities that could affect the disease status or the response to the treatment, 3) missing patient data, incomplete treatment protocol or incomplete patient monitoring.

EXAMINATION – LASER APPLICATION

In order to evaluate the efficacy of SML in the treatment of the non-centre involved CSME properly, we compared the results of the SML with those of the focal laser photocoagulation, the application of which has proven to be an effective and appropriate treatment for this particular condition. More specifically, we examined the change in best corrected visual acuity (BCVA) and the central macular thickness (CMT) after the aforementioned laser treatments.

At the initial visit, a detailed individual and family history was recorded for all patients. BCVA (Greek version of ETDRS chart) (21), CMT estimation using a spectral domain optical coherence tomography (SD-OCT) / scanning laser ophthalmolscopy (SLO) (Spectral OCT SLO, OPKO/OTI, Miami, FL) intraocular pressure (IOP) measurement using a Goldmann applanation tonometer, slit lamp examination and fundoscopy, as well as measurement of hemoglobin A1c (HbA1C) levels, were performed in all patients at the initial and at the 3 and 6 month-post-intervention visits.

The laser application (wavelength of 532 nm, green) was performed with Supra Scan 532 nm laser (Quantel Medical, Cedex, France) in all eyes by the same ophthalmologist as follows:

Laser treatment was performed using 532 nm micropulse laser with an Area-Centralis lens (Volk Optical Inc, Mentor, Ohio, USA). The micropulse 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 200 ms duration in the nasal side outside the vascular arcade with the power titrated from 50 mW upward until a burn became barely visible. To perform the laser treatment, the laser was switched from continuous-wave emission mode to micropulse emission mode at 15% duty cycles and the power was doubled (100 mW) with a 100 ms exposure duration. The spot size was set at 50 to 100 μm and the number of spots varied according to the extension of DME. As regards conventional focal laser photocoagulation, a 50 μm spot diameter and a 100 ms duration was used. The power was adjusted according to each patients' needs.

STATISTICAL ANALYSIS

An a priori power analysis was performed. For an effect size of 0.8, 52 participants would be required, for the study to have a power of 0.8 at the significance level of 0.05. All data were collected in an Excel database and analysed statistically with the same software (Excel 2010, Microsoft Corp, Redmond, WA, USA).

The normality of measured data was evaluated using Kolmogorov-Smirnov test. Normal distribution data were assessed by Student's t-test. Non-parametric data were assessed with Mann–Whitney U test. All statistical tests were two-tailed. P-values less than 0.05 were considered statistically significant.

RESULTS

60 eyes from 60 patients (33 men, 27 women) diagnosed with non-centre involved CSME were included in this study. The mean age of the patients was 67.8 ± 8.05 years. Detailed demographic and clinical parameters are presented in Tables 1 and 2. Non-significant differences were detected with respect to age (p = 0.54), diabetes duration (p = 0.48), HbA1c (p = 0.72), and IOP (p = 0.87) No parameter demonstrated significant differences between the two groups before laser.

Tab. 1 Demographic and general characteristics of the two groups.

Variables		**G1**	**G2**	***p-value***
No.		30	30	
Sex	Male	17 (56.7%)	16 (53.3%)	0.86
	Female	13 (43.3%)	14 (46,7%)	
Mean ± SD				
Age (years)		67.6 ± 7.4	68 ± 8.7	0.54
Diabetes duration (years)		11.5 ± 10	12.5 ± 11	0.48
HbA1c (%)		7.2 ± 1.02	7.4 ± 1.04	0.72
IOP (mmHg)		17.98 ± 2.73	17.81 ± 2.89	0.87

G1: subthreshold micropulse laser Group, G2: conventional laser photocoagulation Group, HbA1c: Hemoglobin A1c, IOP: Intraocular Pressure, SD: Standard Deviation

Tab. 2 Group comparisons before laser.

Parameter (mean ± SD)	**G1**	**G2**	***p-value***
BCVA (ETDRS letters)	72.42 ± 14.50	71.25 ± 11.57	0.73
CMT (nm)	291.93 ± 67.24	303.5 ± 49.31	0.43

BCVA: best corrected visual acuity, CMT: central macular thickness, ETDRS: early treatment diabetic retinopathy study, G1: subthreshold micropulse laser Group, G2: conventional laser photocoagulation Group, SD: Standard Deviation

All comparisons after laser application are presented in Tables 3 and 4. Significant differences among groups' participants were not detected in the BCVA parameter at any timepoint. Indeed, in six months, the difference in BCVA was increased, but not at a significant level (p = 0.09). On the other hand, CMT in G1 was significantly lower 6 months after laser in comparison to G2 (p = 0.04), while no significant difference was detected for CMT in three months between G1 and G2 (p = 0.56).

Tab. 3 Group comparisons (3 months after laser).

Parameter (mean ± SD)	**G1**	**G2**	***p-value***
BCVA (ETDRS letters)	73.58 ± 11.84	70.25 ± 13.52	0.31
CMT (nm)	285.50 ± 87.52	298.67 ± 86.96	0.56

BCVA: best corrected visual acuity, CMT: central macular thickness, ETDRS: early treatment diabetic retinopathy study, G1: subthreshold micropulse laser Group, G2: conventional laser photocoagulation Group, SD: Standard Deviation

With respect to BCVA, participants in G1, treated with SML, demonstrated improved values at all follow-up timepoints, while participants in G2, treated with CLP, demonstrated a slight deterioration 3 months after laser. However, in 6 months, G2 showed a slight improvement in comparison to baseline value. Additionally, participants in

Tab. 4 Group comparisons (6 months after laser).

Parameter (mean ± SD)	G1	G2	*p-value*
BCVA (ETDRS letters)	77.50 ± 10.50†	72.42 ± 12.40	0.09
CMT (nm)	248.83 ± 56.33†	280.50 ± 59.41†	0.04*

BCVA: best corrected visual acuity, CMT: central macular thickness, ETDRS: early treatment diabetic retinopathy study, G1: subthreshold micropulse laser Group, G2: conventional laser photocoagulation Group, SD: Standard Deviation
* P < 0.05
† indicates significant difference with values before laser application

both groups demonstrated improved CMT values at each timepoint (Figures 1 and 2).

Three months after laser, both groups did not present significant differences in both parameters compared to baseline values (BCVA: G1: p = 0.52, G2: p = 0.67 / CMT: G1: p = 0.61, G2: p = 0.64). On the other hand, CMT in both groups was significantly lower 6 months after laser application in comparison to baseline values (G1: p < 0.001, G2: p = 0.002). Moreover, significant improvement was detected 6 months after micropulse laser in G1 regarding BCVA compared to values before laser treatment (p = 0.001), while no significant difference was found at the same timepoint in G2 after conventional focal laser photocoagulation (p = 0.30).

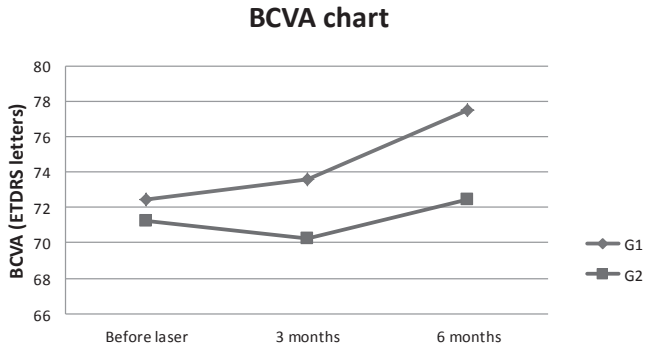
DISCUSSION

Nowadays, approximately 360 million people suffer from DM worldwide (22). By 2030, population with DM is estimated at a half billion (22). DR is a disease with an increasing prevalence in the general population, as average population age and dietary habits have changed. This disease now affects about 93 million people worldwide, of which 17 million suffer from Proliferative Diabetic Retinopathy (PDR) and 21 million from DME (23). Therefore, it is important to develop and apply treatments that are more efficient, accessible, less invasive and with the least possible side effects. Thus, more and more patients will comply with different treatment protocols that can prevent from significant visual loss.

Within this context, the evaluation of the relative efficacy of SML treatment versus CLP for the management of DME has become of major importance to retina specialists. In fact, several studies have dealt with the comparison of SML with CLP. Chen et al. (15) showed that the use of the SML results in slightly better visual acuity compared to the conventional laser, although the differences of the two groups are too small to be of clinical significance. However, according to them the two types of treatment appear to have a similar anatomical effect. Another study by Fazel et al. (24) showed that the SML was more effective than the CLP in reducing CMT and Central Macular Volume (CMV) as well as in improving visual acuity. Qiao et al. (25) reported that the SML results in an equal improvement in visual acuity, contrast sensitivity and reduction of the DME compared to the conventional ETDRS focal photocoagulation protocol, but clearly with less damage to the retina. In addition, other studies (18, 26, 27) showed minimal anatomical, clinically not visible, retinal changes using OCT, microperimetry and fluorescein angiography when a SML treatment was applied confirming the safety of this therapeutic method.

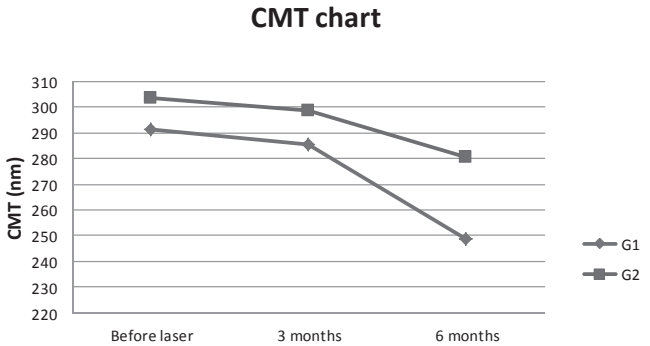
When attempting to interpret former published reports, certain caution should be applied regarding the laser wavelength used. The majority of former investigators have used either 577 nm (yellow) (27–29) or 810 nm (red) (24, 30–34). There are only few studies (16, 20, 35–37) that have used SML of 532 nm (green) for the treatment of DME. However, within the published studies that used 532 nm, three examined the frequency-doubled neodymium: YAG laser of 532 nm (20, 36, 37), while the study of Yu et al. (16), which compared subthreshold 810-nm and 532-nm diode micropulse laser on the retina by histologic examination and differential protein expression, used rabbits' eyes. Finally, Bhatnagar et al. (35) examined if SD-OCT could be used to detect subthreshold retinal burns created using the micropulse diode laser of 532 nm. Consequently, to our knowledge, the present study is the first comparative study that investigates the effect of subthreshold diode laser micropulse in comparison with continuous-wave CLP in the treatment of the non-centre involved CSME in a clinical setting.

Our study outcomes indicated non-inferiority of the SML when compared to continuous-wave CLP. In fact,



G1 = patients underwent subthreshold micropulse laser
G2 = patients underwent conventional focal laser photocoagulation
BCVA = best corrected visual acuity

Fig. 1 Best corrected visual acuity.



G1 = patients underwent subthreshold micropulse laser
G2 = patients underwent conventional focal laser photocoagulation
CMT = central macular thickness

Fig. 2 Central macular thickness.

a potential superiority of the SML has been detected both in the BCVA and CMT at the 6 month-examination point. Specifically, a) G1 participants, treated with SML, appeared a significant improvement of both BCVA and CMT at six months after the laser application, b) while G2 participants revealed a significant improvement at six months only in CMT, c) in fact, at six-month-follow-up, G1 participants had significantly lower CMT compared to patients treated with CLP.

Our promising results indicate the necessity of developing therapeutic guidelines regarding the laser energy, the shot size, the duration and the duty cycle of the SML for the treatment of the CSME. Former studies (38, 39) attempted to compare different laser settings at the same or different wavelengths, however, there is lack of published experience in order to address this significant lack of knowledge in SML treatment. Within this context, further studies and larger cohorts of patients are necessary to confirm our outcomes and contribute to the potential establishment of SML as a reliable treatment option of CSME.

CONCLUSIONS

In conclusion, our results revealed that SML was more effective than CLP in reducing CMT and improving BCVA in patients with non-centre involved CSME. Therefore, it seems that SML can be a good substitute for CLP in CSME treatment if confirmed in future studies, since it is an accessible technology, easy to use and without significant side effects. The use of the SML in an established therapeutic protocol will provide a safe and patient-friendly treatment option, in order to avoid significant visual loss.

FINANCIAL DISCLOSURE

No financial support was received for this study. None of the authors has any proprietary interests or conflicts of interest related to this submission. It is not simultaneously being considered for publication at any other journal.

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