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ORIGINAL ARTICLE

The impact of central foveal thickness on the efficacy of subthreshold micropulse yellow laser photocoagulation in diabetic macular edema

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Abstract

To evaluate the efficacy of short-term subthreshold micropulse yellow laser photocoagulation (SMYLP) on eyes with diabetic macular edema (DME) with different central foveal thicknesses (CFT). Eighty eyes of 40 patients who had previously undergone ranibizumab treatment for DME and who subsequently had recurrent macular edema were included to the study. The study subjects were divided into four groups according to their initial CFT values (group 1, 250–300 μm; group 2, 301–400 μm; group 3, > 401 μm; group 4, 250–300 μm untreated control subjects). Patients were treated with SMYLP for one session and followed for 6 months. All patients underwent complete ophthalmologic evaluation. The alteration from baseline in CFT and the best corrected visual acuity (BCVA) were measured. Patients with a pretreatment CFT ≤ 300 μm experienced the statistically significant reduction in CFT and gain in BCVA at 2 months ($p < 0.05$), whereas patients with baseline CFT > 300 μm experienced no significant change ($p > 0.05$). Hyperautofluorescence lesions, that were not previously described, were detected in fundus autofluorescence imaging in the early period after SYMLP laser and these lesions were regressed with time. Our study indicates that the SYMLP provides a statistically significant improvement in BCVA and a reduction in CFT in the patients with a pretreatment CFT of 300 μm or less in DME and can be safe and effective in mild DME treatment.

Keywords Central foveal thickness · Diabetic macular edema · Micropulse laser · Subthreshold photocoagulation

Introduction

Diabetic macular edema (DME) is the most common cause of vision loss in patients with diabetes mellitus [1]. Laser photocoagulation in the macula has long been recognized as an effective treatment for DME. The Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated a significant benefit of conventional laser (CL) photocoagulation for the treatment of clinically significant macular edema [2]. However, the beneficial effect of CL is associated with the destruction of retinal photoreceptors, progressive enlargement of laser retinal scars, and development of choroidal neovascularization and subfoveal fibrosis [3–6].

Developments in laser technology have led to the development of selective photocoagulation for the retinal pigment epithelium (RPE) via the subthreshold micropulse (STMP) laser photocoagulation method that is designed to target the RPE with minimal effect on the neurosensory retina and choroid [7, 8]. In this modality, the laser energy is transmitted as short pulses (micropulses), which has "on" and "off" cycles rather than as a continuous wave with hundreds of milliseconds cycle duration as with the CL. Heat is distributed by long "off" cycles and energy transfer to the tissue is limited by maximum absorption of the laser energy. This treatment is called STMP laser therapy because no visible scar occurs and the burns remain below the observability limit [9]. Lavinsky et al. performed a pilot study and reported that micropulse laser to be superior to standard modified Early Treatment Diabetic Retinopathy Study (mETDRS) laser in eyes with DME at 1-year follow-up; micropulse-treated eyes gained more vision and had less vision loss than mETDRS-treated eyes [10].

The 577-nm yellow laser light provides peak absorption of oxyhemoglobin, excellent lesion visibility, low intraocular light scattering and pain, and negligible xanthophyll absorption [11, 12]. Additionally, the 577-nm yellow laser wavelength has the advantage of being better absorbed by melanin

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than the 810-nm laser wavelength, a characteristic that is theoretically suited to the micropulse technique aimed at RPE cells [13].

The aim of this study was to evaluate the effects of SMYLP on eyes with recurrent DME previously treated with Ranibizumab and to investigate whether retinal thickness has a role in response to SMYLP.

Material and methods

Study design and patients

This clinical study was carried out from September 2015 to September 2017. The study protocol was approved by the Ethics Committee of the Ankara Numune Education and Research Hospital, and the study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patients prior to enrollment.

Diabetic macular edema was defined as retinal thickening or hard exudates involving the center of the macula. Diabetic macular edema was defined as edema (central foveal T-thicknesses-CFT ≥ 250 μm) involving the central fovea. Patients who had previously undergone ranibizumab treatment for DME and who subsequently had recurrent macular edema were included to the study. Patients were treated with SMYLP for one session. At 2 months after SMYLP, eyes with CFT ≥ 300 μm and loss of ≥ 1 line were treated again with intravitreal ranibizumab.

Patients with a history of CL application, subtenon, or intravitreal steroid injection prior to STMP laser were excluded. Patients with the documented follow-up of < 6 months or missing follow-up appointments were excluded. Patients with simultaneous retinal diseases affecting visual acuities, such as age-related macular degeneration, vein occlusions, vitreomacular tractions, and epiretinal membranes were also excluded.

All subjects underwent a comprehensive ophthalmic examination including best-corrected visual acuity (BCVA) tests using the Snellen chart (20 ft), intraocular pressure measurements, slit-lamp biomicroscopy, and dilated fundus examination. BCVA values were converted to the logarithm of the minimum angle of resolution (logMAR) units for statistical analysis.

Several studies have demonstrated that optical coherence tomography (OCT) can measure retinal thickness in DME objectively and with high accuracy [14, 15].The spectral domain OCT (Spectralis HRA + OCT, Heidelberg Engineering, Heidelberg, Germany) was used to determine CFT before the treatment and at the second, fourth, and sixth months after laser treatment. SD-OCT volume scan (20 × 20 with 49 horizontal sections, ART 15) including en face images and macular mapping image obtained with HRA2 of the macula was performed for each study eye. The retinal thickness map analysis protocol that used in the Early Treatment Diabetic Retinopathy Study (ETDRS) was used for analysis of retinal thickness.

Infrared reflectance (IR) imaging has the potential to show sub-retinal features and pathology by penetrating the retina. IR imaging can be provided during OCT scans. In this study, IR imaging was obtained with Spectralis HRA + OCT.

Fundus autofluorescence (FAF) images were obtained with a confocal scanning laser ophthalmoscope with scanning fields of 50°. For the FAF images, a wavelength of 488 nm was used for excitation with an observation filter passing wavelengths > 500 nm. For FAF images, nine images (8.8 frames per second) were averaged with the automatic real-time composite mode of the instrument to obtain high-quality images. Any possible adverse effects of the laser, including subjective reports of the scotoma, evidence of retinal tissue damage per fluorescein angiography, OCT, or clinical examination were examined.

Patients were divided into four groups based on their initial CFT for more detailed evaluation and more objective evaluation of the laser effect. Group 1 composed of patients with CFT between 251 and 300 μm, group 2 composed of patients with CFT between 301 and 400 μm, and group 3 composed of patients with CFT > 400 μm. Also, 20 eyes with CFT of 250–300 μm DME that did not accept additional treatment were selected as control subjects (group 4). The alteration of CFT and BCVA was measured.

Patients were treated with SMYLP for one session. Macular laser treatment was applied after pupil dilation and topical anesthesia. Laser application was performed with an Area-Centralis lens (Volk Optical, Mentor, OH, USA). SYMLP treatment protocol was performed with a 577-nm yellow light (Supra Scan, Quantel Medical, Cedex, France) with the following parameters: 160-μm spot size on slit lamp, 5% duty cycle of 0.2 s, and zero spacing, and the micropulse laser power used in SMYLP was derived for each eye from a test burn. Laser treatment was performed in all eyes by the same experienced surgeon (MC). The test burn was performed with a 577-nm yellow laser in the continuous-wave mode using a 160-μm spot size and 0.2-s duration outside the vascular arcade with the power titrated from 800 mW upward until a burn became barely visible. Once the thermal threshold was determined for anyone given retina, the power was reduced to 50% of this threshold power for micropulse treatment.

Statistical analysis

The data obtained from the study was entered into the computer and analyzed using the Statistical Package for Social Sciences (SPSS) version 22.0 for Windows (SPSS Inc., Chicago, IL). Descriptive statistics are presented as mean ±

standard deviations, frequency distributions, and percentages. The paired t test was used to compare the alterations in CFT and BCVA from baseline to the second months for each group. One-way ANOVA was used for differences in CFT and BCVA among groups. Additionally, independent sample t test was used to compare the alterations in CFT and BCVA between group 4 and groups 1, 2, and 3. A p value < 0.05 was considered to be significant.

Results

Eighty eyes of 40 patients with the mean age of 57.65 ± 8.45 years (range, 44–73 years) were enrolled to the study. Group 1 composed of 20 eyes, group 2 composed of 18 eyes, group 3 composed of 22 eyes, and group 4 composed of 20 eyes. There were no statistically significant differences regarding the age and sex between the groups ($p > 0.05$). The time between the last anti-VEGF application and micropulse laser treatment was 2–4 months (mean 2.6 ± 1.1 months). Demographic characteristics of patients are shown in Table 1.

The mean overall pre-laser CFT was 343.11 ± 138.57 μm. At 2 months of follow-up, group 1 experienced 37.43 μm reduction in CFT to 238.57 μm (p 0.03) (Fig. 1), whereas groups 2, 3, and 4 experienced no significant change in CFT (p 0.47, p 0.58, p 0.32, respectively). Mean CFT values of baseline and at the second month of follow-up are shown in Table 2.

The mean preoperative BCVA was 0.84 LogMAR. Mean BCVA in group 1 increased from LogMAR 0.52 to LogMAR 0.38 (p 0.01), whereas there were no improvements in BCVA in groups 2, 3, and 4 (p 0.74, p 0.88, p 0.46, respectively). Mean BCVA values of baseline and at the second month of follow-up are shown in Table 2.

At 2 months of follow-up, eyes with CFT ≥ 300 μm and/or loss of ≥ 1 line from the baseline were treated with intravitreal ranibizumab (all cases in groups 2 and 3).

Patients in the group 1 were followed up without any treatment. At 4 months of follow-up, four eyes (20%) had CFT ≥ 300 μm and loss of ≥ 1 line in the group 1 and they required treatment with intravitreal ranibizumab. At 6 months of follow-up, additional four eyes (20%) had CFT ≥ 300 μm and loss of ≥ 1 line in the group 1 and they required treatment with intravitreal ranibizumab.

At 2 months of post-SYMLP laser period, hyperautofluorescent lesions that were not previously described, in FAF imaging were identified (Fig. 2). These lesions were more prominent in infrared imaging (Fig. 3). Over time (at 4 and 6 months), there was the regression in these lesions (Figs. 2 and 3). Scar and atrophic lesions caused by SYMLP lasers were not recorded in each group.

Discussion

STMP laser has gained increasing interest in the treatment of DME with promising results that have been presented in several studies [16, 17].The yellow (577 nm) wavelength occurs outside the absorption spectrum of retinal xanthophylls, potentially allowing for treatment close to the fovea [18]. Retinal thickness may affect the tissue distribution of energy delivered by the STMP laser in a manner that may affect the clinical outcome. In this study, we aim to investigate the influence of initial CFT on the response to 577-nm SMYLP treatment.

In a recent study, Mansouri et al. [19] chose 400 μm to stratify patients into two groups to investigate if the severity of DME influences the effectiveness of 810-nm STMP laser treatment and showed that treatment responses in patients with a pretreatment CFT of greater than 400 μm were worse than those with a pretreatment CFT of less than 400 μm. In our study, patients with a CFT of less than 400 μm were further divided into two groups to investigate this wide range of CFT values in more detail. Our results showed statistically significant CFT reduction and visual gain at 2 months in patients with CFT of 300 μm or less. All cases in groups 2, 3, and 4 were treated with intravitreal ranibizumab at second months. But, patients in group 1 were followed-up without any treatment.

In a study by Kwon et al. [13] evaluating the efficacy and safety of SYMLP in the treatment of DME, the CFT was 385.0 ± 111.0 μm at baseline, and an average CFT reduction of 58 μm was detected in the eyes treated with SYMLP. Of note, in that study, 42.8% of patients had reductions in CFT of > 10% of the baseline thickness, and 57.2% remained the same. When the graphs showing the central macular changes

Table 1 Demographic data of the patients in the four groups

		Group 1 $n = 20$ (eyes)	Group 2 $n = 18$ (eyes)	Group 3 $n = 22$ (eyes)	Group 4 $n = 20$ (eyes)	p value
Age	Mean	57.84	59.78	53.17	60.48	0.74
	Range	47–70	44–73	48–70	46–71	
Gender	Female	10	8	12	12	0.69
	Male	10	10	10	8	

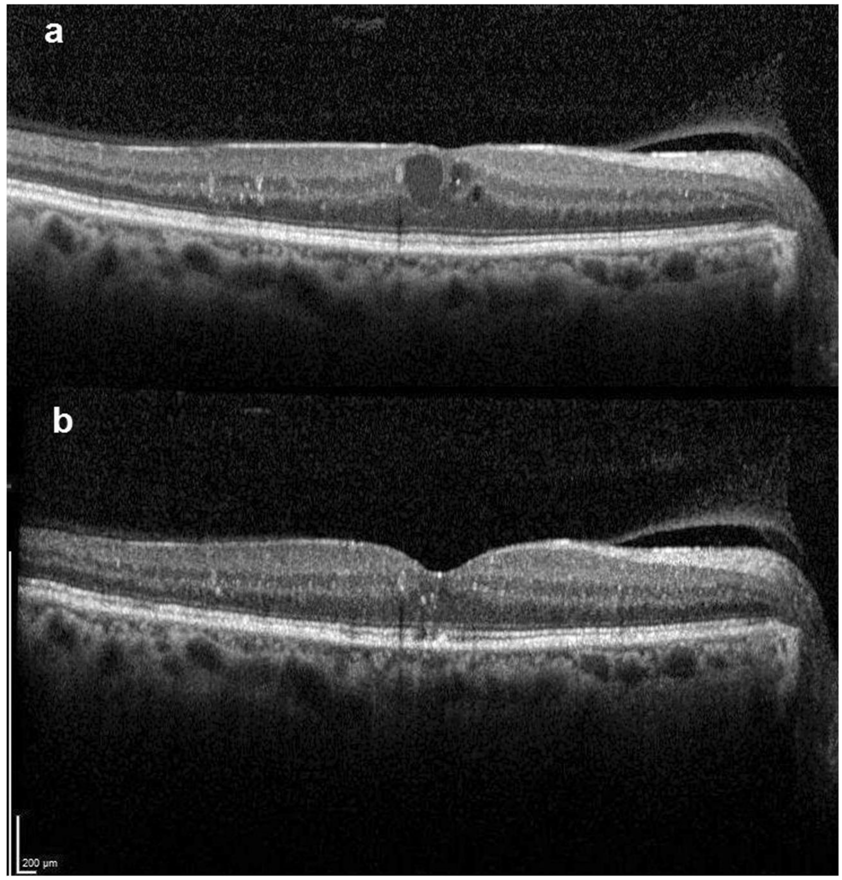

Fig. 1 Optical coherence tomography of a patient that central foveal thickness reduced from 298 μm (**a**) to 265 μm (**b**)

of the cases were examined, it was seen that the treatment response was relatively better when the pretreatment CFT values were 300 μm or less, similar to the values we mentioned in our study.

In previous studies, it was shown that half of the reduction in macular edema was achieved in 2–3 months of post-STMP laser [10, 16]. In the prospective OCT measurement study of Luttrull et al. [20], it was shown that the majority of patients respond in 3 months of post-STMP laser. Figueria et al. [21] showed no further reduction in CFT 4 months of post-STMP laser. Therefore, if there is no improvement in macular edema by 4 months, longer waiting times are unlikely to result in a significant improvement in those who do not respond to STMP.

The exact cause of this lack of response to STMP alone in patients with the severe anatomical disease is not known. It is thought that RPE cell stimulation by laser results in the release of cytokines that reduce the edema and might be responsible for the beneficial effects of STMP [22, 23].Severe edema may possibly dilute the concentration of these cytokines or change the distribution of laser energy throughout the retina and RPE. Patients with greater edema may require different laser parameters. Another option might be to reduce macular edema with anti-VEGF agents or steroids before re-STMP in cases that do not respond to SMTP laser therapy. In our study, if there was persistent DME with CFT ≥ 300 μm, rescue anti-VEGF agent was given instead of re-SYMLP treatment. At fourth month of follow-up, 20% of patients in the group 1 required intravitreal

Table 2 The mean central foveal thickness and best corrected visual acuity of values of baseline and at the second month of follow-up after laser treatment

		Group 1	Group 2	Group 3	Group 4
Central foveal thickness (micron)	Baseline	276.00 ± 22.44 (264–296)	349.62 ± 8.98 (331–389)	454.61 ± 118.23 (425–523)	281.74 ± 32.43 265–289)
	After laser	238.57 ± 25.87 (212–278)	363.87 ± 21.85 (361–416)	563.44 ± 121.94 (434–699)	318.44 ± 44.58 (302–348)
Visual acuity (LogMAR)	Baseline	0.52 ± 0.05	0.69 ± 0.12	1.52 ± 0.33	0.55 ± 0.05
	After laser	0.38 ± 0.04	0.98 ± 0.15	1.69 ± 0.39	0.72 ± 0.06

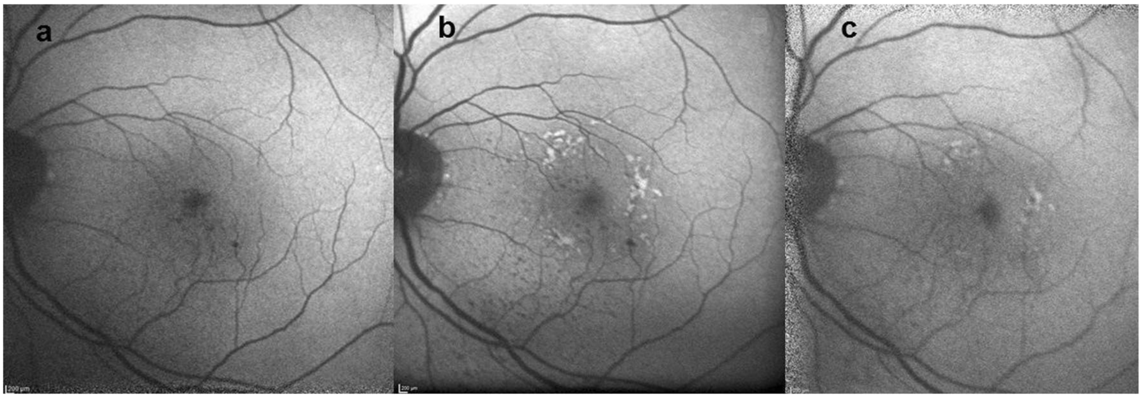

Fig. 2 Fundus autofluorescence (FAF) image of a patient. **a** FAF image of the patient before laser treatment. **b** FAF image of the patient at the second month of follow-up after laser treatment. Hyperautofluorescent lesions were observed. **c** FAF image of the patient at the fourth month of follow-up after laser treatment. Hyperautofluorescent lesions were decreased

injection; at sixth month of follow-up, intravitreal injections were needed for an additional 20% of patients in the group 1. Rescue anti-VEGF injections were less required during the following months in patients with group 1. In the study of Mansouri et al. [19], if there was persistent CSME at 6 months, rescue bevacizumab was given. From 6 to 12 months of follow-up, no patient with pretreatment CFT ≤ 400 μm required rescue anti-VEGF injections versus all the patients with CFT > 400 μm received rescue bevacizumab injections. In our study, re-treatment was performed with CFT > 300 μm for disallowing to anatomical deterioration.

In our study, hyper-autofluorescence lesions, that were not previously described, were detected in FAF imaging in the early period after SYMLP laser and these lesions were regressed with time. Hyperautofluorescent lesions have been described earlier in continuous wave laser photocoagulation as well as for selective RPE laser treatment [24]. They represent RPE damage and re-proliferation but do not distinguish whether photoreceptor damage has occurred or not. We speculated that simple power reduction to 50% from thermal threshold may not be appropriate for the true effect of micropulse laser.

There are several limitations in our present study. Firstly, the number of patients in the study was a relatively small sample size with a short follow-up period (6 months). Secondly, the systemic regulation of diabetes mellitus was not known and blood hemoglobin A1c levels were not measured. Thirdly, the patients treated with ranibizumab were included in the study. Fourthly, re-treatment with ranibizumab was performed with CFT > 300 μm and/or loss of ≥ 1 line from the baseline at second months for disallowing to anatomical deterioration.

Conclusion

The anatomical severity of DME may affect the treatment response to SYMLP. Our study indicates that the SYMLP provides a statistically significant improvement in BCVA and a reduction in CFT in the patients with a pretreatment

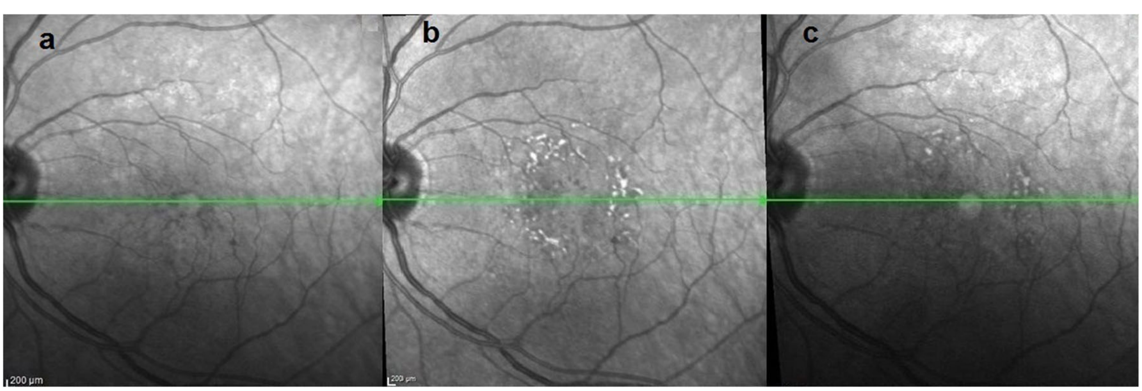

Fig. 3 Infrared reflectance (IR) image of the same patient. **a** IR image of the patient before laser treatment. **b** IR image of the patient at the second month of follow-up after laser treatment. Hyper-reflective lesions were observed. **c** IR image of the patient at the fourth month of follow-up after laser treatment. Hyper-reflective lesions were decreased

CFT of 300 μm or less in DME and can be safe and effective in mild DME treatment. It might also be, that eye with thinner retinal thickness has a better disease activity status and therefore run better with no need of frequent anti-VEGF. Prospective randomized control trials with larger sample sizes and more extended follow-up periods comparing the efficacy of SYMPL laser by the anatomical severity of DME required furthering explaining the optimal role of SYMLP laser in the treatment of DME.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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