

Continuing Medical Education:

Efficacy of subthreshold micropulse laser in the treatment of diabetic macular edema is influenced by pre-treatment central foveal thickness

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Learning objectives

Upon completion of this activity, participants will be able to:

1. Describe the efficacy of STMP as monotherapy for DME in patients with CFT less than 400 μm , based on an interventional case series.
2. Describe the efficacy of STMP as monotherapy for DME in patients with CFT greater than 400 μm , based on an interventional case series.
3. Describe the safety of STMP as monotherapy for DME in patients with CFT both greater and less than 400 μm , based on an interventional case series.

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Efficacy of subthreshold micropulse laser in the treatment of diabetic macular edema is influenced by pre-treatment central foveal thickness

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Abstract

Purpose To determine if the severity of diabetic macular edema influences the effectiveness of subthreshold micropulse (STMP) laser treatment.

Methods A total of 63 eyes of 58 patients with diabetic macular edema were divided into two groups based on their initial central foveal thickness (CFT). Group 1 had CFT $\leq 400 \mu\text{m}$, group 2 had CFT $> 400 \mu\text{m}$. The change from baseline in CFT and visual acuity were compared at 3, 6 and 12 months follow-up. Patients were considered for retreatment with micropulse laser at 3 months if macular edema had not improved. Patients were considered for rescue anti-VEGF injections if there was clinically significant macular edema at 6 months follow-up. Number of laser retreatments, injections, and any adverse effects from STMP laser were recorded.

Results Group 1 ($n = 33$) experienced an average of $55 \mu\text{m}$ reduction in CFT and 0.2log MAR gain in visual acuity at 12 months ($P < 0.001$). No patient required rescue anti-VEGF injections. Group 2 ($n = 30$) experienced no significant change in CFT or visual acuity by 6 months despite retreatment with STMP in 19 eyes. From 6 to 12 months follow-up, all the patients in group 2 received rescue Bevacizumab injections that resulted in $307 \mu\text{m}$ reduction in CFT and 0.3log MAR improvement in visual acuity ($P < 0.001$). No adverse effects from STMP laser were recorded.

Conclusion Severity of edema can influence the effects of STMP laser. STMP monotherapy is safe and effective in treating edema of mild to moderate severity.

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Introduction

Macular edema is the leading cause of vision loss in patients with diabetes.¹ An important component of the treatment for clinically significant diabetic macular edema (CSME) is visible end point laser photocoagulation proposed by the Early Treatment Diabetic Retinopathy Study (ETDRS).² This treatment proved to be an effective method in decreasing the risk of moderate visual loss in patients with CSME. However, the beneficial effect of conventional laser photocoagulation is associated with the destruction of retinal photoreceptors, progressive enlargement of laser retinal scars, and the risk of developing choroidal neovascularization and subfoveal fibrosis.^{3–5}

Unlike conventional laser photocoagulation, where a steady continuous wave laser output is applied, subthreshold micropulse (STMP) laser treatment delivers laser energy by dividing the beam into a train of short laser pulses. Each pulse has an on and off duration. The ratio of on to off time is defined as the duty cycle. A lower duty cycle reduces the laser energy from being

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delivered, thus diminishing the overall thermal effect and allowing tissue temperature to decrease to the baseline prior to the arrival of the next pulse. This method of laser delivery limits the overall laser-induced heat spread to the adjacent tissues and provides a means to deliver the laser energy without the detectable tissue damage associated with standard photocoagulation.^{6–8}

Several prospective randomized trials have reported equal improvement in BCVA and retinal thickness between STMP and conventional ETDRS laser photocoagulation for CSME.^{9–12} In those trials, the average CFT prior to STMP treatment was $<400\ \mu\text{m}$ and the subgroup analysis specifically looking at patients with large CFT was not reported. Retinal thickness may affect the tissue distribution of energy delivered by the STMP laser in a manner that may affect the clinical outcome. To our knowledge, there are no published data comparing the efficacy of STMP laser in accordance with the anatomical severity of macular edema. This is a pilot study to investigate whether retinal thickness has a role in response to 810-nm STMP.

Patients and methods

Institutional review board's approval was obtained for the study through the Western Institutional Review Board, Olympia, Washington. All data were collected in accordance with the Health Insurance Portability and Accountability Act of 1996. We retrospectively reviewed the office charts of patients with the diagnosis of diabetic macular edema (DME) treated with 810 nm STMP laser from January 2012 to March 2013.

Patients with a history of conventional laser application <6 months prior to STMP laser, anti-VEGF injection <3 months prior to STMP, subtenon or intravitreal steroid injection <6 months prior to STMP laser were excluded. Patients with documented follow-up of <12 months or missing follow-up appointments were excluded. Patients with simultaneous retinal diseases affecting visual acuity, such as age related macular degeneration, vein occlusions, and epiretinal membranes were also excluded.

All the patients were treated with the 810-nm diode micropulse laser (IRIDEX Corporation, Mountain View, CA, USA) with the following laser settings: power 950 mw; 300 ms duration; and 5% duty cycle and slit lamp (aerial) spot size of $125\ \mu\text{m}$. Area centralis contact lens (spot magnification factor of 1.06) was used to deliver the laser resulting in retinal laser spot size of $132\ \mu\text{m}$. Laser was applied in a confluent fashion to the entire area of the macular edema and leakage guided by OCT and fluorescein angiography. ETDRS visual acuity, spectral domain OCT (Spectralis HRA + OCT, Heidelberg Engineering, Heidelberg, Germany)

measurements of central foveal thickness (CFT) and follow-up intervals were recorded from patient records. Visual acuities were converted to Log MAR values for analysis. Any adverse effects of the laser including subjective reports of scotoma, evidence of retinal tissue damage per fluorescein angiography, OCT, or clinical examination were recorded.

The decision to retreat with laser was to the discretion of the treating physician. Generally, if macular edema had not improved by 3 months after the initial laser, decision was made to retreat with laser. If by 6 months after the initial laser there was clinically significant macular edema, decision was made to treat with rescue Bevacizumab injection.

Patients were divided into two groups based on their initial CFT. Group 1 composed of patients with CFT $\leq 400\ \mu\text{m}$, group 2 composed of patients with CFT $>400\ \mu\text{m}$. The change from baseline in CFT, and visual acuity were compared between the groups. Analysis of variance was used to compare the change in CFT and visual acuity. Student's *t*-test was used to compare the patient's baseline characteristics. A *P*-value <0.05 was considered to be significant.

Results

One hundred and thirty-four consecutive patients with DME who were treated with STMP laser were identified. Of these, 63 eyes of 58 patients met the inclusion/exclusion criteria. Group 1 composed of 33 eyes of 30 patients and group 2 composed of 30 eyes of 28 patients. Patients' baseline characteristics are shown in Table 1.

At 3 months follow-up, group 1 experienced $41\ \mu\text{m}$ reduction in CFT to $290\ \mu\text{m}$ ($P = 2.6\text{E-}5$), whereas group 2 experienced no significant change in CFT ($605\text{--}608\ \mu\text{m}$, $P = 0.41$). Mean visual acuity in group 1 increased from Log MAR 0.3 (20/40) to Log MAR 0.133 ($\sim 20/27$) ($P = 6.2\text{E-}10$), whereas visual acuity in group 2 remained unchanged at Log MAR 0.54 ($\sim 20/70$) ($P = 0.43$). At 3 months follow-up, 19 patients in group 2 were retreated with STMP laser versus none in group 1. No patient in either group received intravitreal injections.

At 6 months follow-up, group 1 experienced an additional $9\ \mu\text{m}$ reduction in CFT to $281\ \mu\text{m}$. No patient in group 1 had clinically significant macular edema. Group 2 experienced no significant change in CFT ($608\text{--}611\ \mu\text{m}$). Mean visual acuity in group 1 increased to Log MAR 0.1 (20/25). Mean visual acuity in group 2 remained unchanged at Log MAR 0.55 ($\sim 20/70$) (Table 2). Changes in CFT and visual acuity between 3 months follow-up and 6 months follow-up were not statistically significant in either group.

No patient in group 1 had persistent CSME at any time from 6 months follow-up until 12 months follow-up and

Table 1 Patient baseline characteristics

	Group 1	Group 2
Age, years, mean (SD) (Range) $P = 0.87$	58.9 (7) (47–71)	58.7 (6.15) (48–72)
Percent female	47	46
HgA1C %, mean (SD) (Range) $P = 0.54$	8.0 (0.53) (7.2–9.2)	7.9 (0.72) (6.8–9.1)
Duration of diabetes, years, mean (SD) (Range) $P = 0.55$	9.6 (3.51) (5–18)	9.1 (3.1) (5–17)
Percent type II diabetes	97	100
CFT, μm , mean, (SD) (Range) $P < 0.001$	331 (39.4) (276–400)	605 (67.8) (485–731)
Visual acuity, Log MAR, (SD) (Range) $P < 0.001$	0.3 (0.11) (0.1–0.5)	0.54 (0.12) (0.3–0.7)

Abbreviation: CFT, central foveal thickness.

Table 2 Mean (range) CFT and visual acuity at baseline and various follow-up intervals in two groups

	Baseline	3 Months	6 Months	12 Months
Group 1 CFT(μm)	331 (292–400)	290 (265–332)	281 (255–298)	276 (258–296)
Group 2 CFT(μm)	605 (442–858)	608 (445–897)	611 (478–883)	298 (247–329)
Group 1 visual acuity (Log MAR)	0.3	0.13	0.1	0.1
Group 2 visual acuity (Log MAR)	0.54	0.54	0.55	0.24

Abbreviation: CFT, central foveal thickness.

received no intravitreal injections. At 12 months follow-up, group 1 had experienced a total of 55 μm reduction in CFT from baseline (331 μm) to 276 μm ($P = 5.6\text{E}-10$). Mean visual acuity in group 1 was Log MAR 0.1 (20/25). This represented a total of 0.2log MAR increase compared with baseline ($P = 4.2\text{E}-14$).

At 6 months follow-up, all the patients in group 2 had clinically significant macular edema and received monthly rescue Bevacizumab injections until CSME resolved. On an average, group 2 received 3.1 (range of 2–5) injections from 6 months follow-up until 12 months follow-up. At the final follow-up, group 2 experienced a significant reduction in CFT to 298 μm ($P = 5.1\text{E}-30$). Mean visual acuity in group 2 increased significantly to Log MAR 0.24 (~20/34) ($P = 6.7\text{E}-16$).

No adverse effect from STMP laser was recorded in either group. There was no evidence of tissue damage from STMP laser per fluorescein angiography, OCT images, or clinical findings at any follow-up visit.

Discussion

STMP laser has gained increasing interest in the treatment of DME with promising results. STMP has been shown to be an effective treatment option

comparable to the modified ETDRS macular photocoagulation without causing chorioretinal scarring or inducing visual field scotomas. Better transmission of 810-nm light through retina can imply that retinal thickness is not a determining factor for a response to 810 nm STMP laser. Our goal was to investigate the influence of macular thickness on the response to 810-nm STMP laser treatment.

Patients investigated in prior studies^{9–12} had mean CFTs in the range of 250–350 μm and standard deviations in the range of 50–90. This implies that most patients in these studies had CFT < 400 μm and therefore resembled patients in group 1 of our study. We chose 400 μm to stratify patients into two groups based on the authors' own observation that patients with CFT > 400 μm do not respond well to STMP monotherapy.

Our results show an average CFT reduction of 55 μm and two lines of visual gain at 12 months in group 1. No patient in group 1 had retreatment with STMP laser or required rescue anti-VEGF injections. Vujosevic et al¹¹ showed an average CFT reduction of 47 μm in eyes treated with STMP alone. Of note, in that study, the eyes treated with STMP had an average baseline CFT of 358 μm , which is close to that of our patients in group 1.

In studies done by Laursen *et al*⁹ and Lavinski *et al*¹² patients continued to improve for up to 12 months post laser; however, more than half the reduction in macular edema was already achieved by 3 months post laser. Luttrull *et al*¹³ have shown in their prospective OCT measurement study that the majority of patients respond in 3 months post STMP laser. Figueria *et al*¹⁰ showed no further reduction in the macular edema between 4 months post STMP laser and 12 months post STMP laser. Therefore, if there is no improvement in macular edema by 6 months, it is unlikely that waiting longer would result in a significant improvement in non-responders to STMP. In our study, if there was persistent CSME at 6 months, rescue Bevacizumab was given.

The decision to retreat with laser was left to the discretion of the treating physician. Generally, if macular edema had not improved by three months, decision was made to retreat with laser. In group 2, majority of eyes (19 out of 30) were retreated with STMP laser at 3 months. Despite this, all 30 eyes had persistent CSME at 6 months follow-up and required rescue injections of Bevacizumab. The significant reduction in the macular edema which was noted at the final follow-up for group 2 is most likely due to rescue injections rather than delayed effect of laser.

The exact cause of this lack of response to STMP alone in patients with severe anatomical disease is not clear. We are not aware of any study reporting on the treatment effects of STMP alone on the subgroup of patients with severe macular edema. It is possible that the effect of STMP on this subgroup is washed out in reporting averages for the entire group as is customary. Multiple factors could be in play. It is thought that RPE cell stimulation by laser results in the release of cytokines that decrease the edema and might be responsible for the beneficial effects of STMP.^{14,15} Severe edema could possibly dilute the concentration of such cytokines or alter the distribution of laser energy throughout the retina and RPE. Perhaps different laser parameters are required in patients with greater edema. Another option might be to reduce the macular edema with anti-VEGF agents or steroids prior to the application of STMP laser.

The limitations of our study include its retrospective nature and small sample size. Prospective randomized control trials with larger sample sizes comparing different laser power settings and combination regimens are required to further elucidate the optimal role of STMP laser in the treatment of severe DME.

In summary, our pilot study indicates that the anatomical severity of DME can influence the treatment response to STMP laser. STMP laser monotherapy is safe and effective in treatment of mild to moderate DME.

Summary

What was known before

- Subthreshold micropulse (STMP) laser is effective for the treatment of diabetic macular edema without causing retinal damage.

What this study adds

- Severity of macular edema influences the effectiveness of STMP laser.
- Patients with central foveal thickness greater than 400 μm do not respond well to STMP alone.

Conflict of interest

The authors declare no conflict of interest.

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1. Your patient is a 68-year-old man with DME and CFT of 378 μm. According to the interventional case series by Dr Mansouri and colleagues, which one of the following statements about the efficacy of STMP as monotherapy for DME in patients with CFT <400 μm is most likely correct?
 - A At 12 months, average reduction in CFT was 25 μm
 - B At 12 months, average gain in visual acuity was 0.2 log MAR
 - C From baseline to 12 months, change in visual acuity was not statistically significant
 - D Four patients required rescue anti-VEGF injections

2. According to the interventional case series by Dr Mansouri and colleagues, which one of the following statements about the efficacy of STMP as monotherapy for DME in patients with CFT >400 μm is most likely correct?
 - A By 6 months, there was a significant reduction in CFT
 - B By 6 months, there was a significant gain in visual acuity (after retreatment with STMP in 19 eyes)
 - C From 6 to 12 months' follow-up, one-third of the patients in group 2 received rescue bevacizumab injections
 - D Rescue bevacizumab injections resulted in a 307 μm reduction in CFT and 0.3 log MAR improvement in visual acuity ($P < 0.001$)

3. According to the interventional case series by Dr Mansouri and colleagues, which one of the following statements about the safety of STMP as monotherapy for DME would most likely be correct?
 - A Fluorescein angiography at 6 months showed evidence of tissue damage in three patients
 - B Optical coherence tomography images at 3 months showed evidence of tissue damage in two patients
 - C STMP is associated with the destruction of retinal photoreceptors, progressive enlargement of laser retinal scars, and risk of developing choroidal neovascularization and subfoveal fibrosis
 - D STMP delivers laser energy by dividing the beam into a train of short laser pulses, limiting overall laser-induced heat spread to adjacent tissues and avoiding detectable tissue damage

Activity evaluation

1. The activity supported the learning objectives.				
Strongly disagree				Strongly agree
1	2	3	4	5
2. The material was organized clearly for learning to occur.				
Strongly disagree				Strongly agree
1	2	3	4	5
3. The content learned from this activity will impact my practice.				
Strongly disagree				Strongly agree
1	2	3	4	5
4. The activity was presented objectively and free of commercial bias.				
Strongly disagree				Strongly agree
1	2	3	4	5