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Tissue-sparing Micropulse Diode Laser Photocoagulation in Practice

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The treatment of diabetic macular edema (DME) is a long-standing challenge for retina specialists. Since the Early Treatment for Diabetic Retinopathy Study (ETDRS), laser therapy has advanced to offer clinicians more options for their patients, depending on the pathology that is being addressed. Grid patterns, improvements in spot size, and wavelength modifications are among these advances. A persistent issue with laser photocoagulation has been the blanching that results from the intense heat applied by the laser, which kills tissue and creates scars that expand with time. A modified-ETDRS strategy, which uses mild-intensity and low-density laser is an improvement, but still results in damage and scarring. One of the more recent advances in lasers is the introduction of tissue-sparing micropulse technology. Micropulse photocoagulation protocols employ low-intensity, high-density laser applications in envelopes of repetitive short pulses to induce beneficial intracellular anti-angiogenic and restorative biological factors without producing visible signs of laser treatment during or at any time postoperatively. This technology can be paired with the 810 nm and newer 577 nm lasers to produce effective results with a higher level of safety.

The articles in this supplement discuss some of the more recent data and clinical experience using tissue-sparing micropulse laser to treat DME, with additional clinical experience in treating macular edema secondary to branch retinal vein occlusion (BRVO). The beneficial effects of micropulse laser for BRVO with little to no damage to the retina is particularly important in light of the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE)-BRVO study results, which support the use of laser as first-line treatment for BRVO.[1]

The introduction of steroids and anti-vascular endothelial growth factor (anti-VEGF) agents into our armamentaria has also had a dramatic effect on how we treat our patients. Studies such as the Diabetic Retinopathy Clinical Research Network's, which showed that ranibizumab (Lucentis, Genentech) plus prompt or deferred laser provided increased efficacy for patients with DME, have given credence to the use of combination strategies, particularly for diffuse macular edema.[2]

More data are being collected on the efficacy and safety of micropulse laser, but from what we have learned thus far, this technology appears to aid clinicians in maintaining the Hippocratic oath to "do no harm."

—Robert L. Avery, MD

1. Scott IU, Ip MS, VanVeldhuisen PC, Oden NL, et al; SCORE Study Research Group. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular Edema secondary to branch retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 6. *Arch Ophthalmol.* 2009;127(9):1115-1128.
2. Diabetic Retinopathy Clinical Research Network; Elman MJ, Aiello LP, Beck RW, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology.* 2010;117(6):1064-1077.

CONTENTS

Evolving Retinal Laser Phototherapy: Less Damage is Better

BY MARTIN A. MAINSTER, MD, PhD, FRCOphth

Top-down clinical trials have proven the efficacy of retinal laser therapy. *Bottom-up* experimental studies have demonstrated its biological effects. After four decades of successful use, however, there's still no clear scientific explanation of why retinal phototherapy is effective for treating retinal vascular disease.[1]

Numerous clinical trials have shown that less destructive and even nondestructive laser phototherapy can achieve therapeutic goals and still preserve visual sensitivity.

LASER EFFECTS

Laser light can induce beneficial retinal biochemical and physiological changes. Photochemical, photothermal, and photomechanical laser-tissue interactions are all potentially constructive or destructive.[2] Contemporary retinal phototherapy is primarily photothermal in nature.[3,4] Laser-induced retinal temperature increase is proportional to retinal irradiance (power density, power/area), for a particular laser wavelength, spot size, exposure duration, and patient pigmentation.[2,3,5]

Serendipity has played a key role in discovering how laser phototherapy can be used to treat retinal vascular disease. Retinal photocoagulation is unquestionably valuable, but decades after clinical trials established its efficacy, the reasons for its success remain uncertain. Thus, retinal laser procedures still cannot be designed with specific biochemical goals in mind.[1]

WHY HARM THE RETINA?

In the past, many believed that laser therapy had to destroy oxygen-consuming photoreceptors and/or retinal pigment epithelial (RPE) cells in order to be effective. That perspective has been disproven. Numerous clinical trials have shown that less destructive and even nondestructive laser phototherapy can achieve therapeutic goals and still preserve visual sensitivity.[1,6-12]

Experimental studies provide insight into laser therapy's potentially beneficial effects. Photocoagulation upregulates inhibitors and downregulates inducers of vascular endothelial growth factor (VEGF).[13-15] It downregulates matrix metalloproteinases which degrade extracellular matrix and it upregulates their tissue inhibitors, inhibiting the initiation and maintenance of angiogenesis.[16] It induces bone marrow derived stem cells to migrate to laser exposure sites where they can differentiate into and replace dysfunctional or injured cells.[17-19] It also induces RPE apoptosis and neuroprotective heat shock proteins in the choroid, optic nerve, and neural retina.[20, 21] Additionally, it upregulates pigment epithelium-derived factor (PEDF), a powerful inhibitor of angiogenesis.[22]

REDUCING RETINAL DAMAGE

New laser technologies and methodologies can limit photocoagulation damage by (1) using barely visible or subthreshold treatment endpoints, (2) reducing retinal irradiance and thus temperature rise,[23] (3) utilizing very brief, repetitive laser pulses as in micropulse photocoagulation, and (4) optimizing laser treatment wavelength.[4]

Photocoagulation occurs when laser radiation is absorbed primarily by melanin in the RPE and choroid. Light absorption converts laser energy into heat, directly increasing the temperature of exposed pigmented tissues. Heat conduction spreads this temperature rise from light absorbing to contiguous chorioretinal sites. Neural retina overlying exposed pigmented tissue is damaged by heat conduction in suprathreshold photocoagulation, loses its transparency and scatters white slit-lamp light back at an observer. More damage means less transparency and a whiter lesion.[4,24]

Visible lesions are only one type of laser damage threshold and potential treatment endpoint, as shown in Figure 1. Photomechanical effects occur at roughly three times the laser exposure needed for a visible lesion. Invisible lesions that are apparent only with fluorescein or autofluorescence imaging occur at a half

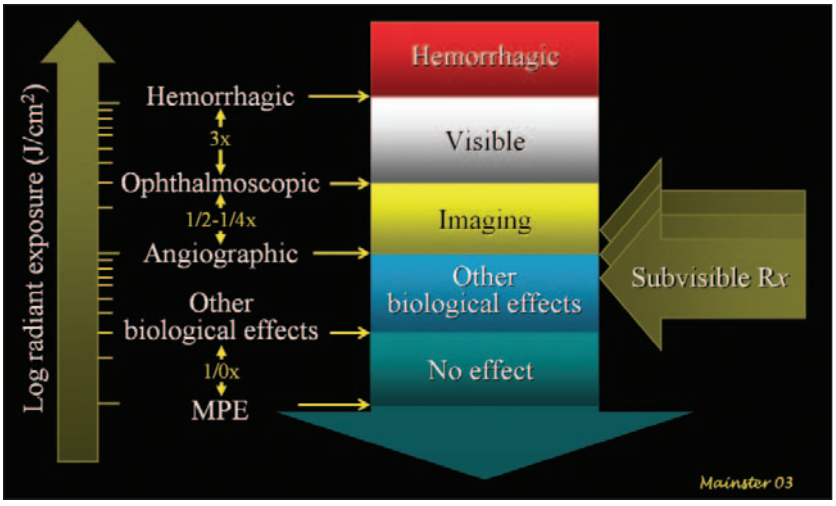

Figure 1. There are different damage thresholds and potential treatment endpoints for clinical laser phototherapy.

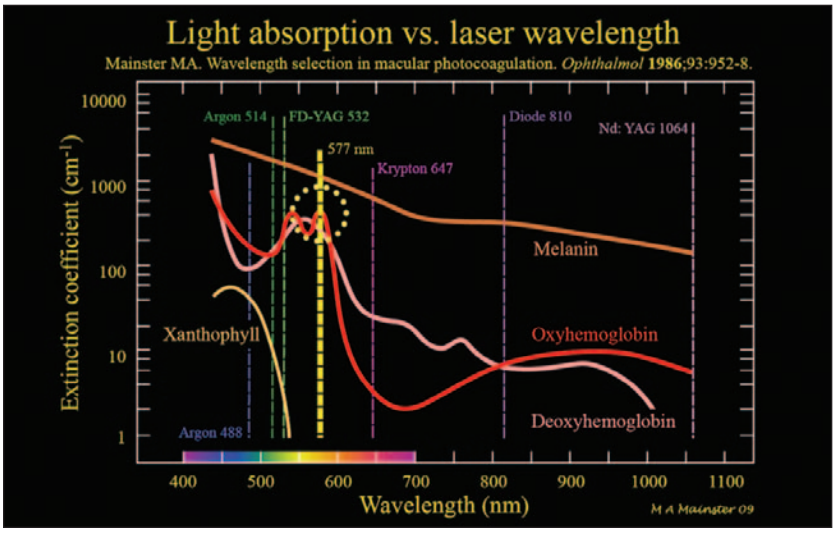

Figure 2. The Iridex IQ 577 photocoagulator exploits the 577 nm yellow peak of oxyhemoglobin to improve the comfort and convenience of standard and micropulse photocoagulation.

to a fourth of the exposure needed to produce ophthalmoscopically visible lesions. Other biological effects including VEGF downregulation occur at even lower laser exposures. In clinical parlance, *subthreshold* means *subvisible*. Smaller retinal irradiances can produce therapeutic effects at lower temperature rises that cause less or no significant retinal damage.[1,4]

LOCALIZING LASER EFFECTS

RPE cells are 10 to 14 µm tall. Localizing thermal effects within them requires laser exposures to be 0.7 msec or shorter. 0.7 msec is 50 times shorter than the shortest exposures available with manual or automated-pattern conventional photocoagulators. Additionally, delivering all the laser energy in a single 0.7 msec pulse can cause hemorrhage and postoperative choroidal neovascularization, one of the reasons that ruby lasers were abandoned early in the evolution of retinal phototherapy.[1,4]

Micropulse photocoagulation provides an effective workaround for this problem. Laser energy is delivered in a burst ("envelope") of micropulses, rather than a single pulse. There is insufficient time for heat conduction to spread temperature rise to adjacent sites, each micropulse denatures only a small fraction of target tissue molecules, and repetitive micropulses combine to produce therapeutic effects.[1,4]

Micropulse photocoagulation has been available for more than 15 years.[25] Clinical trials have demonstrated that it is as effective for treating diabetic macular edema as conventional, more damaging, photocoagulation.[6-12] They also show that it can improve visual sensitivity whereas suprathreshold ETDRS-type photocoagulation decreases it.[6,8] This latter finding is potentially significant in view of recent trials comparing ranibizumab therapy with conventional suprathreshold laser photocoagulation.

VEGF itself may not be an optimal target for treating diabetic macular edema because diabetic macular edema is caused primarily by breakdown of the inner blood retinal barrier in which VEGF's role remains uncertain.[26] More significantly, VEGF is normally expressed in adult retinas, it is an important maintenance factor for Müller cells, the choriocapillaris, and retinal neurons, and it is also a neuroprotectant against ischemic retinal injury.[27-29] The long term consequences of repeated intravitreal anti-VEGF therapy is unknown and a potential issue especially in younger eyes.[26]

OPTIMIZING LASER WAVELENGTH

No controlled clinical trial has ever proven the clinical advantage of one laser wavelength over another in conventional suprathreshold retinal photocoagulation, but dye lasers exploited the 577 nm yellow peak of oxyhemoglobin to improve the comfort and convenience of standard clinical retinal photocoagulation (Figure 2).[3,4] Yellow 577 nm laser light provides excellent lesion visibility, low intraocular light scattering and patient pain,[3] and high choriocapillaris absorption for more uniform effects in

patients with light or irregular fundus pigmentation.

Dye laser photocoagulators were popular in the 1980s and 1990s but became obsolete because of their high initial and maintenance costs. New semiconductor laser devices now provide cost-effective, reliable, solid-state 577 nm yellow laser light. The IQ 577 photocoagulator (Iridex Corporation, Mountain View, CA) uses this semiconductor technology to provide two watts of 577 nm yellow laser light for optimized wavelength (1) standard retinal photocoagulation, (2) micropulse retinal photocoagulation, (3) standard laser trabeculoplasty, and (4) micropulse laser trabeculoplasty.

STAY TUNED...

Despite pharmacological advances, laser treatment remains a critical part of diabetic retinopathy care. Principles for limiting and localizing its effects have been known for decades. Suprathreshold photocoagulation may be a cure but it's also a problem. Contemporary laser technology offers a cure for that problem. As I see it, the goal of 21st Century laser therapy should be the induction of beneficial intracellular biological effects, and destroying retinal cells by laser photocoagulation will eventually prove as unnecessary as medieval bloodletting.[1]

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Tissue-sparing Micropulse Laser in Practice

BY VICTOR CHONG, MD, FRCS, FRCOPHTH

Laser retinal photocoagulation in the macula has long been recognized as the treatment of diabetic macular edema (DME), and macular edema secondary to branch retinal vein occlusion (BRVO). Since the introduction of anti-vascular endothelial growth factor (anti-VEGF) agents and steroids for the indication of treating macular edema, however, the use of laser has been challenged because of the intraretinal scarring and collateral damage that laser has been known to induce. Complications of conventional laser include loss of visual acuity, reduction in color, night, and contrast vision, not to mention more serious complications, which can include choroidal neovascularization, and epiretinal fibrosis.[1,2]

Tissue-sparing laser photocoagulation, or micropulse laser, has been proposed as an alternative to conventional laser to obtain the beneficial effects of laser while minimizing the negative effects. Lanzetta et al[3] suggested that non-ophthalmoscopically visible endpoint photocoagulation may limit the damage to the retinal pigment epithelium (RPE) and thus reduce the amount of injury to the neurosensory retina. Several studies have identified the RPE's role in both vascular endothelial growth factor inhibition and in repair of the inner and outer blood-retinal barrier.[4-7]

This article will discuss my own clinical experience with subthreshold micropulse laser photocoagulation.

Micropulse laser has been proposed as an alternative to conventional laser to obtain the beneficial effects of laser while minimizing the negative effects.

CLINICAL USE OF MICROPULSE LASER

I currently use the IQ 810 nm (Iridex Corporation, Mountain View, CA) for micropulse laser photocoagulation. I have had experience with the 577 nm laser for a few months, but the majority of my experience is with the 810. The majority of my patients are Caucasians, and I use a spot size of 125 µm, and power setting of 1800 mW (maximum) for 200 ms with a 5% MicroPulse duty cycle. For patients of Asian or African origin, I turn the power down to a subthreshold level at 1400 or 1500 mW.

In the past, we applied a test burn using continuous-wave but have found that using the maximum power makes this step unnecessary. The most serious risk when treating below an ophthalmoscopically visible endpoint laser is undertreatment—the micropulse technique induces no permanent laser scars.

I use a dense, contiguous pattern with the laser over the edematous area based on optical coherence tomography (OCT) so I do not deliberately treat microaneurysms as these will be hit with the pattern.

I have recently started treating small foveal cysts, which can cause mild visual loss but can get worse over time. These cysts are commonly associated with microaneurysms very close to the fovea, which are too close to be treated by conventional laser. Micropulse laser does not scar, making this an ideal treatment.

With micropulse laser, we do not want to see any kind of tissue response or color change. On fundus autofluorescence imaging, RPE changes are difficult to interpret because it is unclear whether the changes occurred because of the laser or because of long-standing edema. On fundus photography, angiography, or microscopy, no changes can be detected.

FOLLOW-UP

After I treat with micropulse laser, if there is no foveal involvement, I see the patient back at 6 months. If I was treating a large area of edema, I bring them back at 3 months, as I might need to retreat.

Retreatment is guided by OCT. If the edema appears significantly improved, but not entirely clear on OCT, I will often retreat only the area that remains swollen. If the eye appears to not have responded at all to the first treatment, I will carry out the fluorescein angiography to see if I can detect ischemia or some other reason for the recalcitrant edema.

If the patient has responded well to the first treatment and they have only a small area of edema left, I may choose not to retreat because my experience has been that these patients tend to continue to improve

Now that there are more options for future treatment, the idea of tissue-sparing laser treatment is even more important.

without further treatment.

Patients who have smaller areas of edema at the first treatment are generally seen back at 6 months, because I can be confident that the first micropulse laser applications were successful.

My protocol for retreatment does not differ from the first treatment. The only difference that exists is that I am usually treating a smaller area the second time around.

COMBINATION THERAPY

The use of micropulse laser alone is restricted to non-fovea involving edema, or focal edema with very limited foveal involvement. In the case of diffuse edema, I use intravitreal anti-VEGF agents and micropulse laser starting together.

TREATMENT PEARLS

Applying micropulse laser is easy, despite some misconceptions. The most important factor is that the user must be on focus during the entire treatment. With a conventional laser treatment, if the user cannot detect any color change, the laser is most likely out of focus. With micropulse, however, there is no color change, so it is important to concentrate during the treatment. However, an extra safety margin exists with the micropulse technique, allowing the spots to be closer to one another.

GENERAL CONSIDERATIONS

In this era of anti-VEGF, it is important to remember that laser still plays a role in treating retinal diseases. For example, when macular edema is present and foveal involvement is either nonexistent or limited, there is no reason to commit patients to repeated intravitreal injections of anti-VEGF agents.

Applying standard green laser, however, causes scarring; if the patient's vision deteriorates further in the future, anti-VEGF agents will not be of use and the scarring often expands over time. Now that there are more options for future treatment, the idea of tissue-sparing laser treatment is even more important. The English National Screening Programme for Diabetic Retinopathy has resulted in many more patients presenting with non-foveal involving DME. Although the United States does not have a national screening program, there are plenty of screening initiatives in place throughout the country, and more of these patients are presenting there as well.

More data are required on the efficacy of micropulse laser for non-foveal involving DME and for combining anti-VEGF agents with micropulse laser for diffuse DME, but my clinical experience shows promise for the successful treatment of these conditions without the collateral damage that has been seen with conventional laser.

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Subthreshold Micropulse Laser Treatments Proved Safe and Effective

REPORTS ON TWO STUDIES AND AN INTERVIEW WITH EDOARDO MIDENA, MD, PHD

Subthreshold micropulse diode laser therapy is as effective as modified Early Treatment Diabetic Retinopathy Study (ETDRS) laser photocoagulation for the treatment of clinically significant diabetic macular edema (DME) without visible damage to the retinal pigment epithelium (RPE), according to a 2010 study by Vujosevic et al.[1] The study authors compared best corrected visual acuity (BCVA), microperimetry, and fundus autofluorescence (FAF) after subthreshold micropulse diode laser and modified ETDRS laser treatments.

METHODS

The study was a prospective randomized clinical trial that evaluated 62 eyes of 50 patients who underwent treatment for untreated, center-involving DME. Prior to laser treatment, all patients were examined for BCVA and underwent examination with slit-lamp biomicroscopy, FAF, optical coherence tomography (OCT), microperimetry, and fluorescein angiography (FA). All testing was repeated at months 1, 3, 6, 9, and 12, excluding FA, which was performed at baseline, 6, and 12 months. Patients were required to have BCVA of ≥35 ETDRS letters (logMAR ≤1.0) and foveal thickening ≥250 µm on OCT for inclusion in the study. Thirty-two eyes were treated with subthreshold micropulse diode laser using the OcuLight SLx 810-nm diode laser (Iridex Corporation, Mountain View, CA) and 30 were treated with modified ETDRS laser using the Coherent Novus Omni 514-nm green laser (Coherent, Palo Alto, CA). The treatment parameters for subthreshold micropulse diode laser were a 125-µm spot size, 5% duty cycle, 200 ms envelope duration, 750 mW power, and varying number of confluent spots to cover the area of clinically significant macular edema (CSME) up to 250 to 300 µm from the center of the foveal avascular zone (FAZ). The treatment parameters for modified ETDRS were a 100-µm spot size, 100 ms durations, 80 mW to 100 mW power, and a varying number of spots spaced 2 burns diameter, according to the extension of CSME.

RESULTS

The 12-month BCVA was stable in both groups (mean 0.21 ±0.3 logMAR in the subthreshold micropulse diode laser group and 0.29 ±0.3 logMAR in the ETDRS group) and there was no significant change from baseline at any of the follow-ups. There was a significant decrease in mean central retina thickness (CRT) in both groups (P=.0002 in the micropulse group and P=.0001 in the ETDRS group), but the difference in CRT at 12 months between the two groups was not statistically significant (358.3 µm ±93.7 µm in the subthreshold micropulse diode laser group and 378.4 µm ±94.5 in the ETDRS group; P=.26).

On FAF, none of the eyes from the subthreshold micropulse diode laser group showed any changes after treatment and retreatment. All of the eyes from the ETDRS group, however, demonstrated increased FAF patterns throughout the 3-, 6-, and 9-month follow-ups. The FAF patterns decreased at 12 months in six of the eyes, but remained increased in 24 of the eyes.

When FA) was performed at the 12-month point, there were no signs of laser treatment in the subthreshold micropulse diode laser eyes vs the ETDRS eyes, of which all showed visible scarring on FA.

CONCLUSIONS

"Our FAF and microperimetry data are in favor of subthreshold micropulse diode laser toward ETDRS photocoagulation treatment in patients with center-involving CSME," the authors concluded. "Additional studies on larger samples and with longer follow-ups are needed to assess standardized parameters and to better understand the mechanisms of actions of subthreshold micropulse photocoagulation treatment."

SUBSEQUENT FINDINGS

These findings were reinforced by a study that was recently presented at the 34th Annual Macula Society meeting. Midena et al[2] evaluated in vivo laser-tissue interactions after subthreshold micropulse diode laser was used to treat DME in 25 patients. The treatment parameters were a 125-µm spot size, 5% duty cycle of 200 ms, and 750 mW power. The tissue-laser interactions were measured using BCVA, microperimetry, three spectral-domain (SD) OCT devices, and FAF. Dr. Midena, who presented these data, reported that at 3 months, BCVA was stable in all of the patients and there was significant improvement in central retina sensitivity detected by microperimetry. FAF did not change from

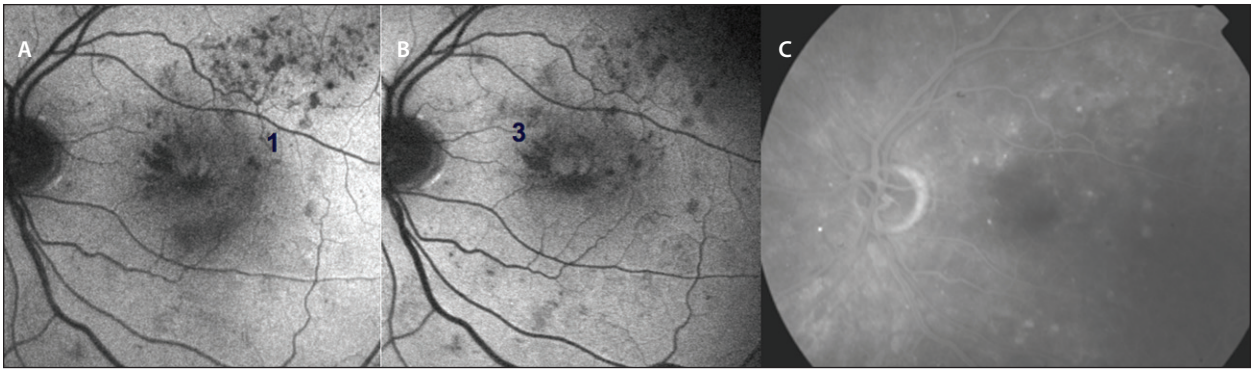

Figure 1. Pre- (A) and post-subthreshold micropulse diode laser (B) treatment for DME. Fundus autofluorescence (FAF) imaging showing no changes. No changes due to subthreshold micropulse diode laser spots are visible on fluorescein angiography (FA) (C).

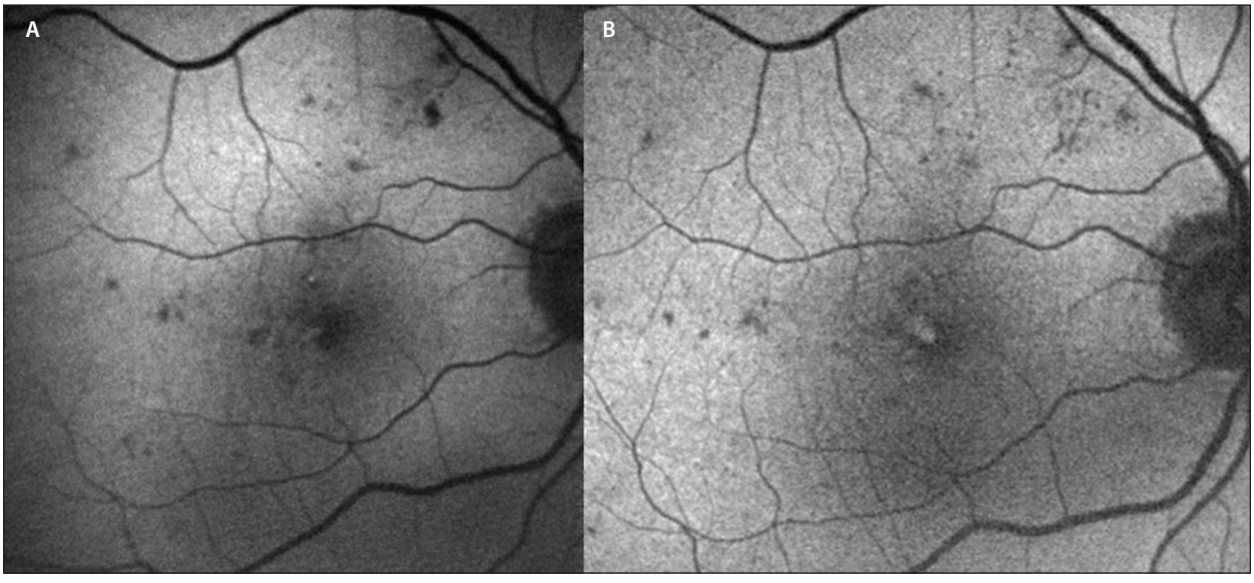

Figure 2. Pre- (A) and post-subthreshold micropulse diode laser (B) treatment for DME. FAF imaging shows no changes after 6 months.

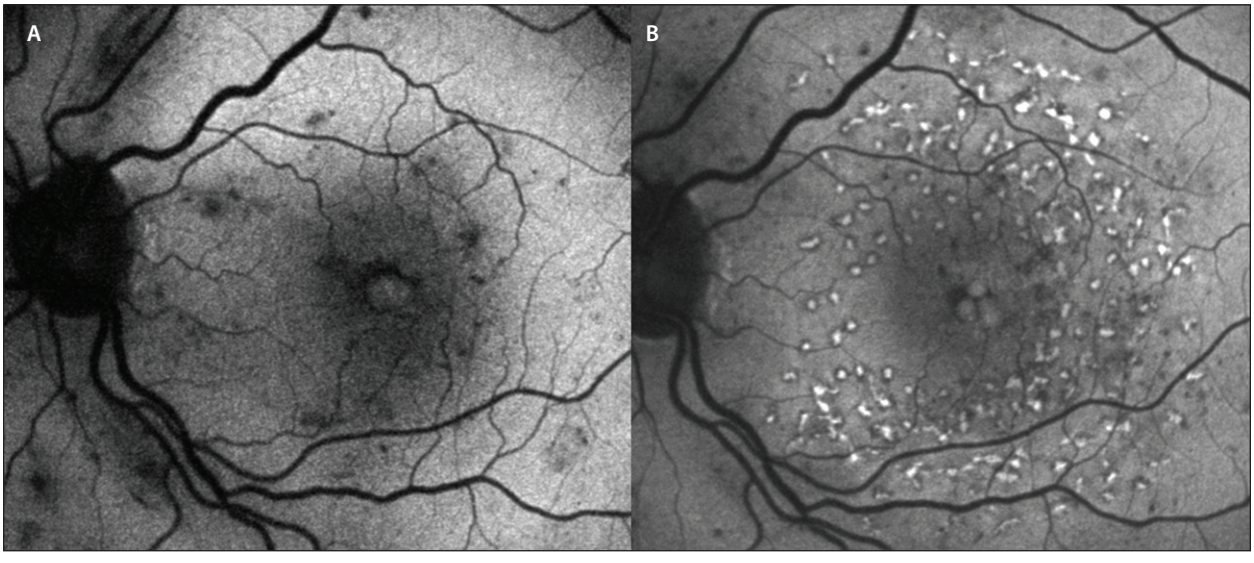

Figure 3. Pre (A) and post-modified-ETDRS (B) treatment for DME. FAF imaging shows hyperfluorescent spots corresponding to laser spots. Some of these hyperfluorescent spots may eventually become hypofluorescent during follow-up.

baseline, and while SD-OCT showed a significant reduction in CRT at 3 months, there was no detectable morphologic changes to the RPE using any of the three machines. These findings demonstrate that subthreshold micropulse diode laser is effective in reducing DME and maintaining stable BVCA while not inducing any damage to the RPE.

Retina Today recently had the opportunity to speak with Dr. Midena regarding his clinical use of subthreshold micropulse diode laser.

RT: What are your settings on the IQ 810 laser (Iridex Corporation, Mountain View, CA) in clinical practice?

Edoardo Midena, MD, PhD: We use the same settings as we did in our studies: 125-µm spot size, 5% duty cycle, 200 ms envelope duration, and 750 mW power.

RT: Do you apply a test burn?

Dr. Midena: I do not. Our experience from the clinical trial as well as our clinical experience and analysis of the previous literature led us to determine that the 750 mW at a 5% duty cycle would not result in any damage to the RPE, so there is no need for a test burn.

RT: What pattern are you using when performing micropulse therapy? Do you treat microaneurysms?

Dr. Midena: With micropulse, we use contiguous spacing. We treat microaneurysms, but not separately. This was also our experience with ETDRS laser.

RT: Have you seen any kind of tissue response on FA or FAF?

Dr. Midena: We have not (Figures 1-3). If we saw tissue response then we would know that the treatment was not subthreshold. Even with spectral-domain OCT, we have seen no evident changes at the level of the RPE.

RT: What are your follow-up and retreatment protocols?

Dr. Midena: We have been following more or less the same protocol that we use for standard modified ETDRS laser. We see the patient at 3 months post-laser and if we see any edema that meets the requirements for treatment, we retreat following the same protocol as the first treatment.

RT: In your clinical experience, what are the key differences between subthreshold micropulse diode laser and modified ETDRS laser?

Dr. Midena: After completing the clinical trial more than 1.5 years ago, we no longer used modified ETDRS laser treatment as first line. For DME with less than 400 µm of edema, we use subthreshold micropulse diode laser as our first line of treatment because we know it is effective and does not damage the retina.

RT: What cases are you treating with subthreshold micropulse diode laser?

Dr. Midena: Most of the cases that we are treating with subthreshold micropulse diode laser are eyes with DME, either those previously treated with ETDRS laser or those that are treatment-naïve. We treat some eyes with macular edema secondary to branch retinal vein occlusion and some cases of central serous retinopathy using the same approach as we use for DME. We also use micropulse for cases of neurosensory detachment of the retina due to chronic retinal pigment epithelium disorders in the macular area. The subthreshold approach has proved effective for any type of macular edema of a vascular origin.

RT: Can you share any clinical pearls for using subthreshold micropulse diode laser?

Dr. Midena: I would not recommend using subthreshold micropulse diode laser for macular edema thicker than 400 µm, as it will have little impact. Rather, I would suggest that the clinician use either an intravitreal corticosteroid or an intravitreal anti-vascular endothelial growth factor agent to reduce the thickness and then apply subthreshold micropulse diode laser a few weeks later to address the edema. I regularly employ this type of combination therapy in eyes that have a CRT of 400 µm or greater.

RT: What are the implications of the studies that you have conducted evaluating subthreshold micropulse diode laser?

Dr. Midena: In these studies, we did not see changes at the level of the RPE in the follow-up from subthreshold micropulse diode laser on FA, OCT, and even FAF. We consider it to be an important finding that the photoreceptors at the neurosensory level of the retina are not damaged with this laser treatment. It appears that with subthreshold micropulse diode laser, we now have the ability to treat macular edema with laser and have the eye recover from a pathologic state with no scarring, which is a vast improvement over our previous laser treatments.

Edoardo Midena, MD, PhD, is Professor and Chairman of the Department of Ophthalmology at University of Padova in Italy. He reports no financial interests. Dr. Midena can be reached via email at edoardo.midena@unipd.it.

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577 nm Micropulse Laser Treatment of Macular Edema Secondary to Branch Retinal Vein Occlusion

BY NATALIA PASECHNIKOVA, MD, PhD; AND SVIATOSLAV SUK, MD, PhD

Branch retinal vein occlusion (BRVO) is the second most common cause of retinal vascular abnormality after diabetic retinopathy and a frequent cause of visual loss. Population-based studies have reported a prevalence of 0.6% to 1.6% and an incidence rate of 2.14 per 1,000 people aged 40 and older.[1]

Laser treatment has proved to be effective in the treatment of macular edema secondary to BRVO in a number of studies, the most significant being that of the multicenter BRVO study group.[2] The BRVO evaluated whether grid macular laser photocoagulation improved visual acuity in patients with vision of 20/40 or worse resulting from macular edema secondary to BRVO. Study results showed the high efficacy of laser treatment in resolving macular edema and in improving visual acuity compared to no laser treatment. The grid laser group had statistically significant improvements in visual acuity with 65% treated vs 37% controls gaining two or more lines of vision over consecutive visits. Further recommendations included that treatment should be postponed for 3 months after

SUMMARY OF EXPERIENCE AND PARAMETERS USING 577 NM MICROPULSE LASER THERAPY: SVIATOSLAV SUK, MD, PhD

Laser: IQ 577

Power setting: Customized, based on individual fundus pigmentation, CRT, and ocular media transparency.

Test burn: Performed in an area of non-edematous retina outside the arcades, nasal to the optic disc, using a continuous-wave emission with the following parameters:

- **CW exposure duration:** 200 ms
- **Spot size on slit lamp adapter:** 100 µm
- **Contact lens:** Reichel-Mainster (1.05x laser spot)
- **Power:** Titrate the power upward to find the power needed for a barely visible tissue reaction

Subthreshold macula treatment: Grid spaced 1 burn diameter apart as per the BRVO study protocol over all the edematous area using the MicroPulse emission mode at 15% duty cycle with the following parameters:

- **MicroPulse envelope duration:** 200-300 ms
- **Spot size on slit lamp adapter:** 100 µm (Same as test spot)
- **Power:** 2x the power determined from test burn (Power ranged from 200 mW to 400 mW.)
- **Treatment pattern:** Grid pattern spaced 1 burn diameter apart based on BRVO study protocol
- **Tissue response at time of treatment:** None
- **Evidence of laser on FA or fundus autofluorescence:** None
- **Follow-up:** Monthly
- **Re-treatment:** At 3 months if needed

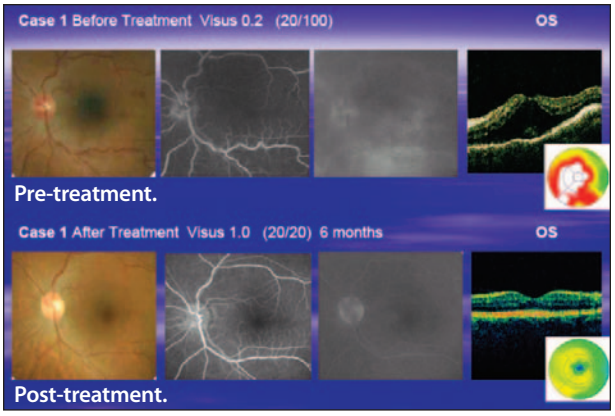

Figure 1. Pre- and post-treatment FAs and OCTs of eye treated with micropulse laser for macular edema.

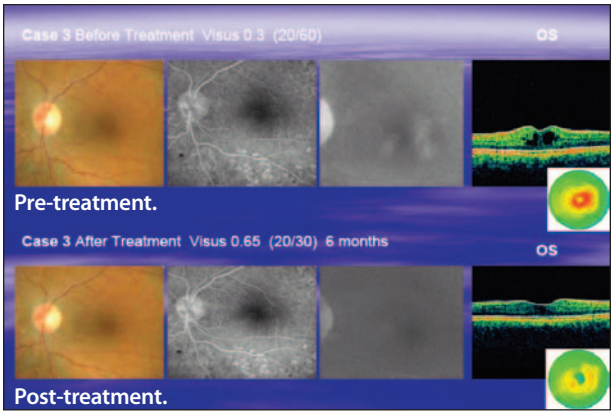

Figure 3. Micropulse laser successfully treated exudative changes due to BRVO, and FA shows no signs of laser damage.

the onset to allow for any spontaneous resolution to occur and to allow some reduction in hemorrhage. Laser treatment was delivered using conventional grid argon green laser with an ophthalmoscopic endpoint visible at the time of the laser application. However, it is well known that laser treatment to a visible endpoint may bring about several complications over the long-term, such as scar enlargement,[3-5] subretinal fibrosis[6,7] choroidal neovascularization,[8] and field sensitivity deterioration[9] which can severely affect visual function.

ADVANCEMENT IN LASER TECHNOLOGY

With the advancements in laser technology, physicians have the ability to achieve good therapeutic results using subthreshold (ophthalmoscopically subvisible) protocols to minimize iatrogenic damage. The IQ 577 yellow laser (Iridex Corporation, Mountain View, CA) is one such promising advancement for the treatment of macular edema secondary to BRVO. Selectivity of the 577 nm yellow wavelength offers the highest oxyhemoglobin-to-melanin absorption ratio, negligible absorption by xanthophyll pigments, and low light scattering of laser radiation, requiring overall less power for similar photothermal effects.[10] The IQ 577 yellow laser features an optional

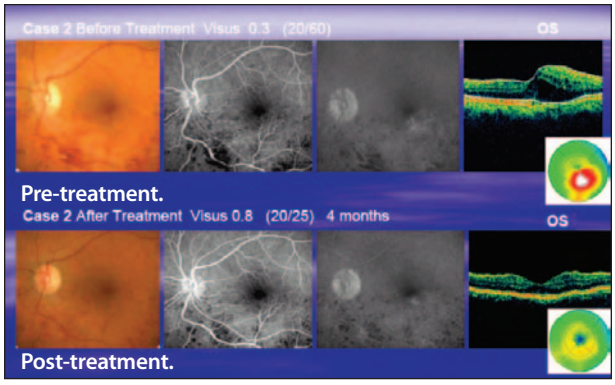

Figure 2. Micropulse laser was used to treat macular edema secondary to BRVO. Vision and edema improved, but FA shows residual exudative changes.

MicroPulse treatment mode that "chops" the continuous-wave emission into a series of short (microsecond) pulses that provides finer control of thermal elevation in the target tissue.

CASE EXAMPLES WITH 577 NM MICROPULSE LASER

We have performed several cases with the 577 nm laser in the MicroPulse mode for macular edema secondary to BRVO with good results. To follow are three cases for which we have used this technology.

Our method of the energy selection was to first apply a test laser burn in the area of non-edematous retina. I set the slit lamp adapter at a 100 µm spot and the laser to continuous-wave emission mode, and then titrate the power upward for a barely visible tissue reaction. Next, I switch the laser to MicroPulse mode set at 15% duty cycle and double the power determined from the test burn and perform grid-type treatment on the macula as recommended by the BRVO study group (see sidebar).

In the first case (Figure 1), exudative and cystoid changes are clearly shown on fluorescein angiography (FA) and optical coherence tomography (OCT). Visual acuity before the treatment was 20/100. Six months after 577 nm micropulse laser, FA and OCT showed full regression of macular edema according to FA, and visual acuity improved to 20/20. FA does not indicate any features typical of conventional laser treatment, ie, laser burn damage or retinal pigment epithelial (RPE) atrophy.

The second case (Figure 2) was one of lower temporal BRVO in the left eye with less pronounced exudation and visual acuity reduced to 20/60. Four months following 577 nm laser treatment in the MicroPulse mode, vision improved to 20/25 and significant reduction in the edema on OCT was observed. The FA, however, showed remaining residual exudative changes.

The third case (Figure 3) was a patient who had previously undergone conventional laser photocoagulation in the affected vascular arcades. The patient had residual exudative

changes in the central zone for the past 12 months caused by the lower arcade BRVO. Prior to treatment with 577 nm laser in the MicroPulse mode, the visual acuity was 20/60. Six months after treatment, regression of the exudative changes in the macular zone were recorded on FA and OCT along with a visual acuity improvement to 20/30. FA completed after treatment does not indicate any signs of laser damage.

CONCLUSION

The therapeutic effects of laser photocoagulation for macular edema secondary to BRVO are well known. To have a laser treatment that provides the standard efficacy in reducing edema and exudation and improves visual acuity without causing scarring or RPE damage is ideal. It is our opinion that studies should be initiated and conducted to evaluate the 577 nm laser in the MicroPulse mode for producing effective results of laser with a minimization of the negative effects in the treatment of macular edema secondary to BRVO.

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Sviatoslav Suk, MD, PhD, is with the Eye Microsurgery Center, Laser Unit, in Kiev, Ukraine. He reports no financial interest. Dr. Suk can be reached via email at laser_dep@mail.ru.

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Infrared Laser in the MicroPulse Mode for the Treatment of Diabetic Macular Edema

BY SERGIY RYKOV PROF, MD, PHD; AND STANISLAV SAKSONOV, MD

It is well known that diabetes is a major cause of retinal vasculature pathology and diabetic retinopathy, which includes diabetic macular edema (DME), and is one of the leading causes of blindness in the world. The incidence of DME over a 10-year period has been reported to be between 13.9% and 25.4% of people diagnosed with diabetes mellitus.[1] Laser photocoagulation currently remains the gold standard of treatment for DME, showing efficacy in many studies, the most notable of which is the Early Treatment for Diabetic Retinopathy Study (ETDRS).[2] Conventional laser photocoagulation is effective, but also associated with well-known collateral effects including functional complications such as scotoma formation and contrast sensitivity reduction.[3] Thus, research is ongoing for methods of laser treatment of the central area of the retina that can reduce collateral anatomical damage and functional loss.

SUBTHRESHOLD MICROPULSE LASER

The aim of our study was to compare the efficacy of subthreshold diode-laser micropulse (SDM) photocoagulation with the 810 nm laser with no visible endpoint to that of traditional 532 nm green focal/grid laser photocoagulation (modified ETDRS protocol) with visible burn endpoint in the treatment of DME. We included 44 eyes of 38 patients with DME; 24 eyes of 18 patients were treated with modified ETDRS focal/grid laser photocoagulation and 20 eyes of 20 patients were treated with SDM photocoagulation. The majority of patients in both groups had previously undergone laser photocoagulation with the modified ETDRS protocol, but not less than 6 months prior to entering this study. Our research did not cover patients with areas of nonperfusion in the macular area, glaucoma, and proliferative changes. All patients went through a compulsory set of examinations including visual acuity, contrast sensitivity testing, biomicroscopy, fluorescein angiography (FA), and optical coherence tomography (OCT) at baseline, months 1, 3, 6, and 12.

Patients in the modified ETDRS group were treated

SUMMARY OF EXPERIENCE AND PARAMETERS WITH SDM: STANISLAV SAKSONOV, MD

Laser: IQ 810

Power setting: Customized, based on individual fundus pigmentation, CRT, and ocular media transparency.

Test burn: Performed in an area of non-edematous retina outside the arcades, nasal to the optic disc, using a continuous-wave emission with the following parameters:

- **CW exposure duration:** 200 ms
- **Spot size on slit lamp adapter:** 125 µm
- **Contact lens:** Reichel-Mainster (1.05x laser spot)
- **Power:** Titrate the power upward to find the power needed for a barely visible tissue reaction

Subthreshold macula treatment: Grid with spots spaced two spot diameters apart as per the modified ETDRS protocol over all the edematous area using the MicroPulse emission mode at 15% duty cycle with the following parameters:

- **MicroPulse envelope duration:** 200-300 ms
- **Spot size on slit lamp adapter:** 125 µm (Same as test spot)
- **Contact lens:** Reichel-Mainster (1.05x laser spot)
- **Power:** 2x the power determined from test burn
- **Treatment pattern:** Modified ETDRS grid
- **Tissue response at time of treatment:** None
- **Evidence of laser on FA or fundus autofluorescence:** None
- **Follow-up:** Monthly
- **Re-treatment:** 3 months if necessary and according to modified ETDRS protocols

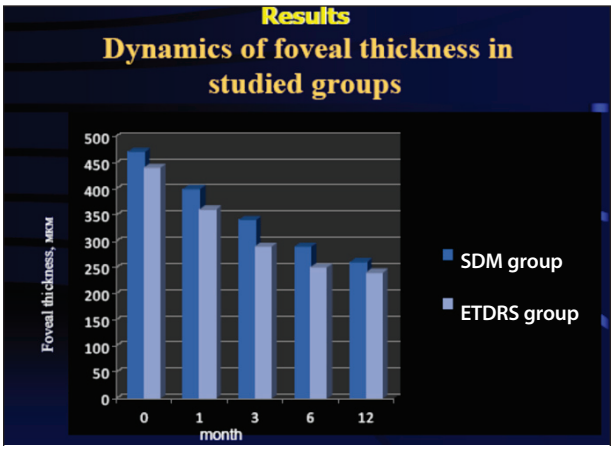

Figure 1. Foveal thickness decreased in both the ETDRS and SDM-treated groups.

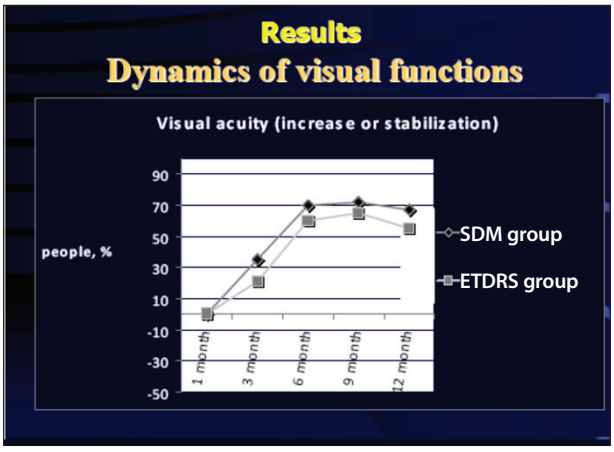

Figure 2. By month 12, visual acuity remained stable (<10 ETDRS letters) or improved (≥10 ETDRS letters) in 70% of cases in both the ETDRS-and SDM-treated groups.

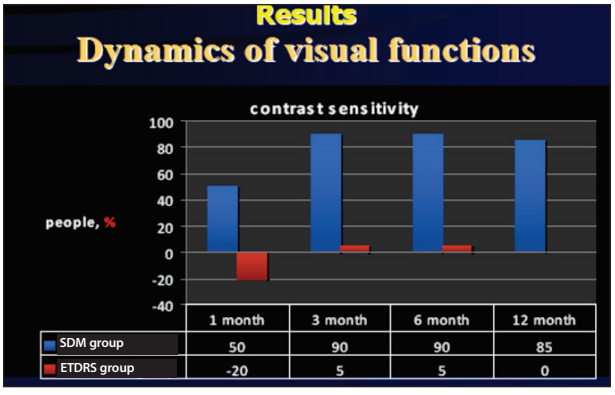

Figure 3. The contrast sensitivity scores for the SDM-treated group remained significantly better than the ETDRS-treated group throughout the follow-up period.

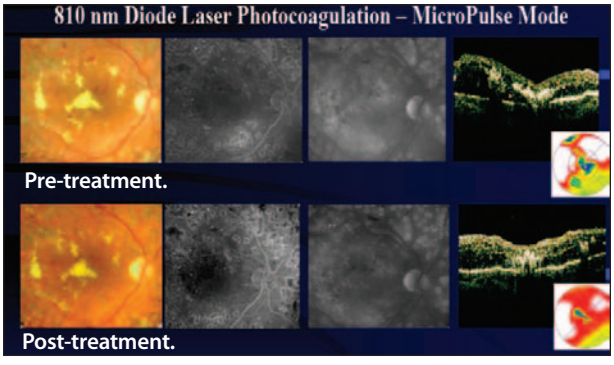

Figure 4. SDM photocoagulation. Patient was previously treating with ETDRS. After SDM photocoagulation, visual acuity stabilization with improvement of macular edema was achieved.

with a grid pattern spaced 1 burn diameter apart using a 100 µm aerial (105 µm retinal) spot size and 50 mW up to 250 mW power until the first signs of blanching in red-free filter were observed. Microaneurysms received a single focal treatment (whitening of the microaneurysm is not necessary).

Patients in the SDM group were treated using the IQ 810 infrared diode laser (Iridex Corporation, Mountain View, CA). Our method to determine the individual laser parameters for each patient's subthreshold treatment included a test burn performed in an area of non-edematous retina outside the arcades, nasal to the optic disc, using a continuous-wave emission and titrating the power upward for a barely visible tissue reaction. Subthreshold treatment over the area of macular edema was then delivered switching the laser to the MicroPulse emission mode set at 15% duty cycle and doubling the power determined from the test burn (see sidebar). With this method, each patient received a subthreshold power based on individual eye conditions (fundus pigmentation, ocular media). Theoretically, the leakage and retinal thickness should not have influenced the laser parameters because 810 nm infrared laser energy can pass through ocular media opacities and edema without substantial absorption and scattering.

RESULTS

The results of our study indicate that, in the treatment of DME, SDM photocoagulation is at least as effective as conventional modified ETDRS focal/grid photocoagulation. Foveal thickness decreased in both groups, as shown in Figure 1. It was our impression that in some patients, the response of retinal edema regression in the macular area was faster in the modified ETDRS group than in the SDM group, although by month 12, the regression of exudative changes became identical in both groups. This could be explained by considering that the ETDRS high-intensity treatment has a larger thermal expansion than the lower intensity SDM treatment, which should have been performed with a higher density grid as demonstrated by Lavinsky.[4]

The dynamics of visual acuity were also comparable in

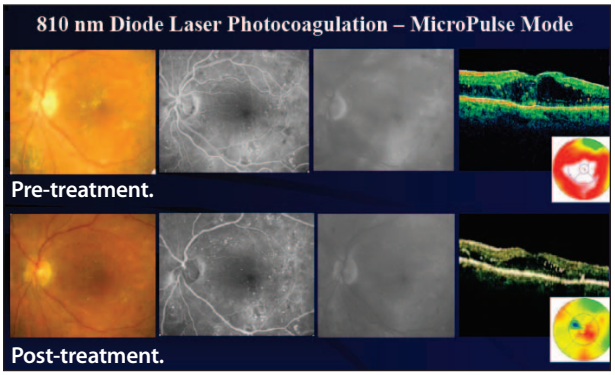

Figure 5. SDM photocoagulation. FA and OCT illustrate the regression of macular edema and the absence of laser burns after SDM treatment.

the follow-up periods, as reported in Figure 2, showing that visual acuity remained stable (<10 ETDRS letters) or improved (≥10 ETDRS letters) in 70% of cases in both the ETDRS-and SDM-treated groups by month 12.

Conversely, contrast sensitivity improved in the SDM group while the modified ETDRS laser group demonstrated a reduction in contrast sensitivity immediately after the treatment, with restabilization over the follow-up period. The contrast sensitivity scores for the SDM group remained significantly better throughout the follow-up period (Figure 3).

CASE EXAMPLES

Figure 4 illustrates a patient who received SDM photocoagulation treatment achieving visual acuity stabilization with improvement of macular edema, as shown on FA and OCT. Visible laser burns from the previous modified ETDRS laser treatment are shown by FA, but no more additional burns have been caused by the subsequent SDM treatment.

Figure 5 illustrates another patient who underwent treatment with SDM (first-line treatment). The FA and OCT images pre- and post-treatment illustrate the regression of macular edema after treatment and the absence of laser burns that would be seen with traditional ETDRS laser photocoagulation.

Figure 6 demonstrates SDM as a first-line treatment for severe DME. The FA and OCT images show good resolution of the macular edema with no retinal scarring evident on the FA.

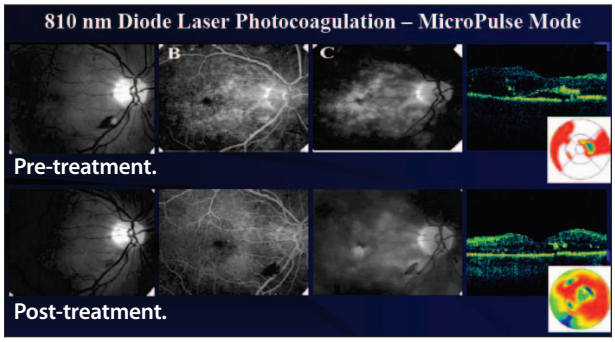

Figure 6. SDM photocoagulation as a first-line treatment for severe DME. Good resolution of the macular edema with no retinal scarring was achieved.

CONCLUSION

In our study, SDM photocoagulation for DME showed results comparable to traditional, modified ETDRS focal/grid laser in visual acuity and CRT at 12 months follow-up. SDM provides stability or improvement of visual function in the majority of cases while reducing iatrogenic anatomic and functional damage, and avoiding all complication and collateral effects of traditional laser photocoagulation. Additionally, we showed that SDM is effective in eyes that had been previously treated with modified ETDRS laser, as well as in eyes treated for the first time. ■

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Laser for BRVO: History and Current Practice

Subthreshold diode micropulse laser therapy avoids thermal injury.

BY JEFFREY K. LUTTRULL, MD

Branch retinal vein occlusion (BRVO) is the second most common retinal vascular disease after diabetic retinopathy, affecting approximately 180,000 people in the United States each year. Risk factors for retinal vein occlusions (RVOs) include glaucoma, older age, and systemic conditions such as diabetes, hypertension, systemic vascular disease, and smoking status.[1,2]

Although many treatments for BRVO have been tried, none was found to be effective before the Branch Vein Occlusion study was begun in 1977. That study, after a mean follow-up 3.1 years in 139 eyes randomized to argon laser photocoagulation or control, found a statistically significant improvement in visual acuity from baseline in treated eyes (P=.0005).[3]

The BVOS investigators in 1984 recommended argon laser photocoagulation for treatment of macular edema due to BRVO, and to this day laser photocoagulation remains the standard care for the condition.

In recent years, there has been increasing interest in addressing macular edema due to BRVO pharmacologically. Several case reports and small series suggested that intravitreal injection of triamcinolone acetonide could be effective in reducing edema in patients with BRVO. However, a large-scale, controlled clinical trial[4] failed to show an advantage of triamcinolone injection over standard laser treatment.

The SCORE-BRVO study[4] compared the safety and efficacy of intravitreal injection of 1 mg or 4 mg triamcinolone to standard care with grid photocoagulation in eyes with macular edema secondary to BRVO. In 411 patients randomized to one of three treatment groups, there were no significant differences between the groups in the primary outcome measure of gain in visual acuity of 15 or more letters at 1 year. However, the rates of adverse events, particularly elevated intraocular pressure (IOP) and cataract development, were higher in the 4-mg triamcinolone treatment group than in the other two groups.

The SCORE-BRVO investigators concluded that grid photocoagulation remains the standard of care for patients with visual acuity loss associated with macular edema secondary to BRVO, and that laser photocoagulation should still be the benchmark against which other treatments for BRVO are evaluated.

Recently it was recognized that vascular endothelial growth factor (VEGF) is an important stimulus of macular edema in RVOs,[5] and as a results there has been increased interest in the use of VEGF inhibitors for the treatment of BRVO. The BRAVO trial[6] showed promising safety and efficacy results at its 6-month primary endpoint, with visual improvements seen in patients treated monthly with intravitreal injection of ranibizumab (Lucentis, Genentech). However, although rescue laser was allowed in the trial, the design did not include a laser-alone arm for comparison. This, along with the need for longer-term results with VEGF inhibition, still leaves us with laser photocoagulation as the standard of care for BRVO.

SUBTHRESHOLD (SUBVISIBLE) DIODE MICROPULSE LASER

The studies cited above each employed conventional suprathreshold thermal laser photocoagulation, the principles of which have remained remarkably unchanged since the days of the Diabetic Retinopathy Study[7] and the Early Treatment Diabetic Retinopathy Study.[8] In these landmark studies it was noted that, in general, treatment efficacy increased with treatment density, while treatment complications increased with treatment intensity. In subsequent years, practitioners have modified these classic photocoagulation techniques hoping to improve the safety of treatment, primarily by reducing treatment intensity. The micropulsed diode laser, developed in the 1990s, is one tool that has been employed to this end.

However, when micropulse diode lasers became available, most practitioners continued using these instruments with the same mindset: The aim of the therapy was still to make burns—albeit less intense—in the retina, as it was assumed that thermal retinal destruction was necessary to achieve the desired therapeutic effect. The persistence of thermal chorioretinal damage dictated continued use of traditional grid and modified-grid treatment techniques to minimize the risk of treatment-associated visual loss.

In 2000, when I started using this technology (IQ 810

laser, Iridex Corporation, Mountain View, CA), I took a different approach. My intent was avoid any burns, to perform an effective treatment that caused no thermal retinal damage. To this end I developed a new treatment technique aimed at maximizing the potential benefits of the micropulsed diode laser for retinal vascular disease, termed low-intensity/high-density treatment. With reports beginning in 2005, my colleagues and I were able to show that this new approach to subthreshold (subvisible) diode micropulse laser photocoagulation (SDM) was effective in the treatment of clinically significant diabetic macular edema (DME) and proliferative diabetic retinopathy without any detectable laser-induced retinal damage.[9-13] Subsequent randomized clinical trials have confirmed our findings in the treatment of diabetic macular edema.[14-16]

SDM offers a number of advantages over conventional thermal laser. Because of its unique safety profile, SDM can be used to treat patients earlier because there is no risk, possibly improving treatment outcomes. Due to the absence of retinal damage, retreatment can be performed as necessary without limit.

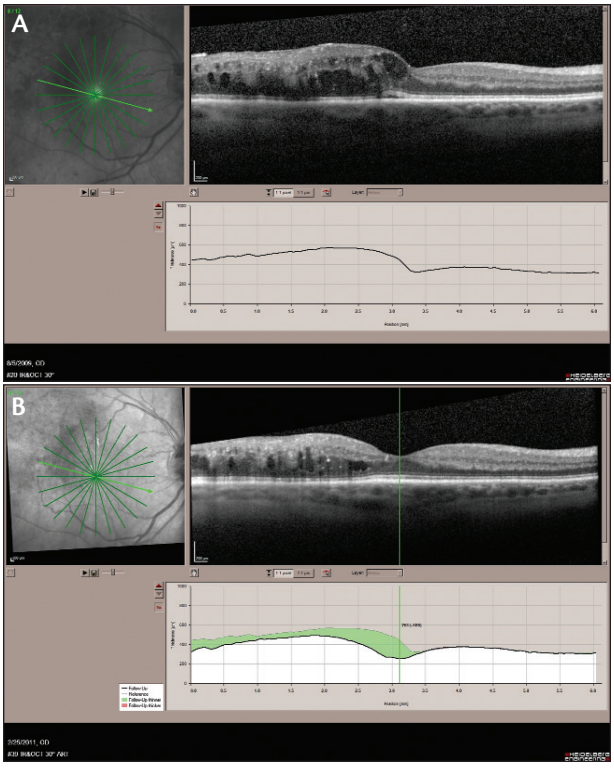
Additionally, SDM can be combined with pharmacologic therapy, such as steroid or anti-VEGF agents, for retina-sparing disease management. The optimal timing and sequencing of drug and laser treatments to achieve complementary and/or synergistic action and avoid inadvertent inhibition of either treatment is likely important, but unknown. In the absence of thermal retinal injury, SDM appears to work by altering retinal pigment epithelial (RPE) cytokine production. Thus, I generally wait at least 1 month between SDM and drug administration to minimize the risk of the drug "cancelling out" the effect of laser treatment.

Unlike conventional argon laser, the diode laser, operating at 810 nm in the infrared, easily penetrates the retina and retinal blood while targeting the RPE. This difference in wavelength and retinal penetration provides a number of clinical advantages over conventional laser. SDM treatment can be performed without waiting for retinal hemorrhage to clear, a common challenge in BRVO. It also means that treatment intensity does not have to be increased to penetrate a markedly thickened macula. For macular SDM treatment, I use exactly the same parameters on every patient regardless of retinal thickness or fundus coloration.

CLINICAL OBSERVATIONS: SDM FOR BRVO

I now have 11 years experience with SDM as my exclusive laser treatment modality for treatment of retinal vascular disease, including treatment of BRVO (Figure 1).

SDM can be effective for the treatment of macular edema and neovascularization due to BRVO. While the response to retinal ischemia in BRVO is likely the same as



Figures 1. Spectral-domain OCT of an eye before (A) and after (B) SDM treatment for BRVO. Note reduction in macular edema without laser-induced retinal damage.

in diabetic retinopathy (increased RPE VEGF production, for instance) the cause is different. Thus, in my experience, macular edema due to BRVO is more likely to wax and wane with more frequent recurrences over a long period of time compared with DME. In addition, because SDM induces a drug-like effect, in some cases it can seemingly wear off. Thus, I find that SDM retreatment and combination therapy are more commonly needed in the management of BRVO than DME. Once again, however, at the end of the day SDM allows me to effectively manage the complications of BRVO without any retinal damage.

Early in my experience with SDM I tended to retreat in 8 to 12 weeks if the macular edema was not completely resolved. Now I follow with spectral-domain optical coherence tomography and re-treat only if there is no response or actual worsening. It is common to observe progressive resolution of macular edema from diabetes or BRVO for as long as 2 years following a single SDM treatment session. Like many others, I tend to use combination therapy more often in eyes with severe center-involving macular edema and/or poor visual acuity in an attempt to accelerate visual recovery.

Finally, high-density/low-intensity SDM may possibly be superior to conventional laser for treatment of BRVO. This may in part be due to the absence of thermal tissue damage and subsequent inflammation that can compro-

mise the effectiveness of treatment. In addition, Parodi and colleagues[17] compared the effects of standard grid subthreshold micropulse diode laser to standard grid conventional laser treatment in patients with BRVO. They found that resolution of macular edema and visual acuity were similar with the two techniques, but the subthreshold technique was not associated with biomicroscopic or angiographic signs. However, subsequent studies of high-density/low-density SDM for DME have found SDM superior to conventional modified ETDRS and normal density micropulsed diode laser treatment.[14-16] I suspect this may hold true in the treatment of macular edema due to BRVO as well.

CONCLUSIONS

It cannot be overstated how the safety and unique clinical characteristics of SDM change one's approach to patient management and conception of photocoagulation for retinal vascular disease, including the treatment of macular edema due to BRVO. SDM offers a perfect first-line treatment because it does no harm. Treatment can thus be initiated earlier and does not have to be delayed waiting for clearance of retinal hemorrhage. Therapy can subsequently be escalated, depending on how the patient responds, by repeating SDM and/or adding a pharmacologic therapy. Mounting evidence for the safety and efficacy of subvisible retinal phototherapy for retinal vascular disease, such as SDM, challenges the continued use of conventional retina-destructive laser techniques. This is an exciting time in the evolution of laser therapy for retinal vascular disease for both retinal surgeons and their patients. ■

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