Subthreshold Micropulse Laser Therapy for Retinal Disorders

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Subthreshold, or tissue-sparing, laser therapy is a subject of interest to retinal specialists worldwide. Today, micropulse technology with 810 nm and 577 nm lasers is used to produce a therapeutic treatment without inducing intraretinal damage detectable on clinical examination during or after treatment. The controlled laser delivery of micropulse technology affords treatment options for diabetic macular edema (DME), proliferative diabetic retinopathy (PDR), central serous chorioretinopathy (CSR), macular edema secondary to branch retinal vein occlusion (BRVO), and even glaucoma. This review will explain micropulse technology and focus on its benefits and challenges in the treatment of retinal disorders.

BACKGROUND

Since its inception, retinal photocoagulation has become more refined, effective, and safe. It has become the first line of treatment for numerous chorioretinal disorders, and its efficacy has been validated by many clinical studies. Laser photocoagulation may produce its therapeutic effects by destroying oxygen-consuming photoreceptor cells and retinal pigment epithelium (RPE), thereby reducing the hypoxic state of the retina. This concept is increasingly being challenged as therapeutic agents such as steroids and anti-vascular endothelial growth factor (anti-VEGF) agents can reduce edema without destroying photoreceptors.

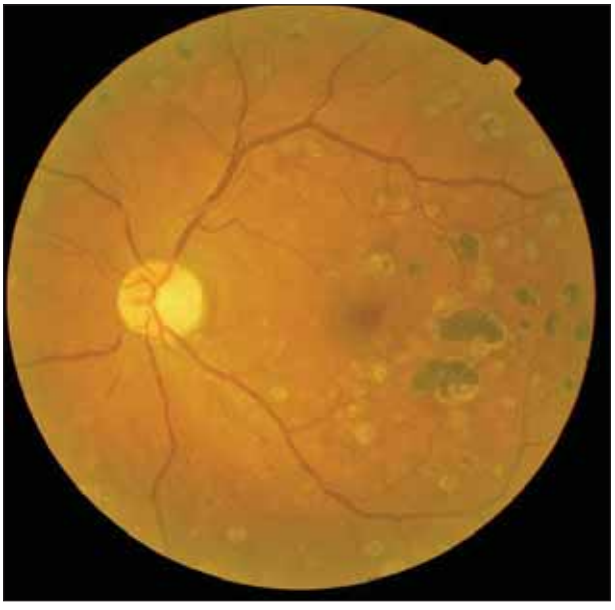

Figure 1. Heavy laser burn.

The heat from conventional laser therapy is conducted to surrounding structures such as the neurosensory retina and the choroid, which can result in collateral thermal

damage (Figure 1). The "grayish" endpoint of a conventional retinal laser burn signifies that the thermal spread has reached the overlying neurosensory retina with a temperature high enough to damage the natural transparency of the retina. This blanching is typically associated with a temperature rise of 20° to 30°C above baseline body temperature.

Complications that have been associated with the use of conventional lasers for retinal photocoagulation include reductions in visual acuity,[1,2] visual field,[3,4] color vision,[2,3,5,6] night vision,[7-9] and contrast sensitivity.[5,10] Other complications include choroidal neovascularization (CNV), hemorrhage, epiretinal fibrosis, and serous detachment of the peripheral retina.[11]

It has, however, been suggested that full thickness retinal damage may not be needed to obtain beneficial effects from laser.[12] The benefits might be due to the up- and down-regulation of angiogenic growth factors (eg, VEGF)[13-16] mediated by the biological reaction of RPE cells that have been only sublethally injured. The RPE plays a significant role in repairing the outer and inner blood-retinal barrier, regardless of the type or location of the laser application. Photothermal elevation that does not produce visible intraretinal damage during or after laser treatment may be termed *subthreshold* laser treatment. Emerging evidence suggests that subthreshold laser treatment may be as effective as conventional laser treatment but with less iatrogenic damage to the tissues surrounding the area of the burn in the RPE.[17-22]

Various optical and thermodynamic principles can be applied to minimize retinal damage.[23] Modifying laser parameters—eg, decreasing wavelength, spot size, retinal irradiance, and pulse duration—may help limit retinal damage. Changing the clinical endpoint from a visible laser burn to an invisible subthreshold application, achieved with micropulse laser treatment, may also reduce retinal damage. The absence of a visible burn means that fluorescein angiography or indocyanine green might be required to detect lesions, and some lesions may not be detectable at all postoperatively.

HOW MICROPULSE TECHNOLOGY WORKS

Using a micropulse mode, laser energy is delivered with a train of repetitive short pulses (typically 100 to 300 microseconds "on" and 1700 to 1900 microseconds "off") within an "envelope" whose width is typically 200 to 300 milliseconds.[24] Micropulse power as low as 10% to 25% of the visible threshold power has been demonstrated to be sufficient to show consistent RPE-confined photothermal effect with sparing of the neurosensory retina on light and electron microscopy.[25] Tissue-sparing protocols are designed to produce only subtle thermal elevations with effects that are invisible during treatment and remain so thereafter. The inner retinal temperature must remain below the threshold of coagulative damage for the retina to maintain its natural transparency. Instead of delivering the requisite energy with a single, high peak power pulse, a series of repetitive, low-energy pulses are used. A four- to ten-fold reduction in the required energy per pulse has been experimentally found with repetitive microsecond pulses, or micropulses, when passing from the visible damage threshold to subthreshold (invisible) damage levels, detectable only with microscopy in histology[25] (Figure 2). Lower energy per pulse reduces peak power, lowers the risk of hemorrhage, decreases the temperature buildup per pulse, and ultimately results in improved confinement of photothermal effects.[12] Absence of chorioretinal laser damage may permit high-density therapy with confluent applications over the entire edematous area and retreatment of the same areas. This may be particularly useful for the as-needed treatment of macular edema.

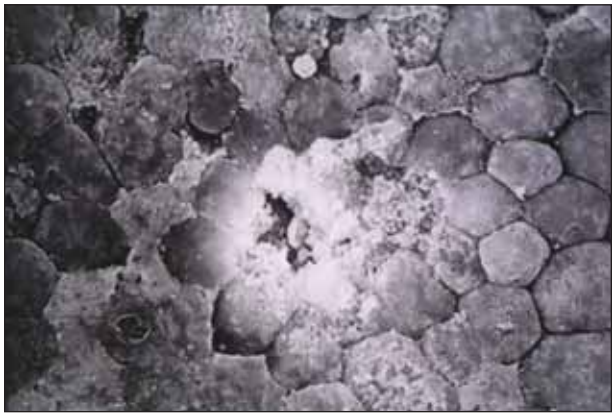

Figure 2. Scanning electron microscopy shows that RPE cell damage was restricted to a small number of cells after micropulse laser treatment.

DOSIMETRY WITH TISSUE-SPARING THERAPY

When treating below an ophthalmoscopically visible endpoint, the question of laser dose is raised. In the absence of permanent laser scars, the most serious risk is undertreatment. Micropulse has no reported complications or collateral effects; therefore, the future of this application will be to fine-tune optimal settings, as nonresponders have been the primary clinical concern.

Retreatment is thought to be feasible because micropulse treatment does not produce chorioretinal scars that could expand or increase the risk of CNV.

Figure 3. Color fundus image of patient treated with micropulse laser: preoperative (A), at 4 months postoperative (B), and at 12 months postoperative (C). No visible scarring can be observed despite the reabsorption of the exudate and edema.

RETINAL APPLICATIONS FOR TISSUE-SPARING THERAPY

Diabetic macular edema. Since the Early Treatment Diabetic Retinopathy Study showed that laser photocoagulation reduced the risk of moderate visual loss by 50% in eyes with clinically significant macular edema, laser treatment has become the standard treatment for DME. Micropulse has been shown to be as effective as conventional argon laser for DME.[1,26,27] Changes in macular sensitivity, as measured by microperimetry, may be evident as early as 1 month after micropulse laser treatment, before significant optical coherence tomography (OCT) changes in retinal thickness are identified.[28] The potential for confluent therapy may be particularly valuable for the retreatment of persistent or new macular edema (Figure 3).

> Micropulse has been shown to be as effective as conventional argon laser for DME.

In the anti-VEGF era, the role of laser requires further examination. Using a laser, which can cause retinal scarring, may no longer be acceptable. Committing patients to multiple injections with non-foveal-involving DME or foveal-involving DME without visual loss, however, would be difficult to justify. Therefore, subthreshold tissue-sparing therapy may play a significant role in these patients.

Proliferative diabetic retinopathy. A small number of studies describe a favorable response using micropulse for panretinal photocoagulation (PRP).[29,30] Luttrull et al[29] found that the response to micropulse laser was similar to that of conventional laser but developed more slowly and without marked contraction of the neovascular tissue. They suggested that this might be useful for patients with extensive active neovascularization, who may be more prone to retinal detachment after conventional PRP. This treatment could also be considered for patients with severe nonproliferative diabetic retinopathy to prevent proliferative diseases.

Central serous chorioretinopathy. The majority of CSR cases resolve spontaneously, but patients with a chronic course threatening visual acuity may benefit from standard laser treatment or photodynamic therapy (PDT). Both of these treatment forms, however, have drawbacks. Traditional laser may cause symptomatic scotomas, CNV, foveal distortion, or subretinal fibrosis. PDT may cause RPE atrophy, transient central scotoma or choroidal hypoperfusion. Micropulse, in contrast, has been shown to enable complete resorption of fluid within 1 month of treatment, and this effect was maintained at 4 months without any clinically discernible evidence of laser-induced iatrogenic damage.[31]

Macular edema due to BRVO. Micropulse laser appears to be as effective as conventional laser in the treatment of macular edema due to BRVO, but it acts more slowly.[32] The use of intravitreal triamcinolone 2 weeks before micropulse treatment for macular edema due to BRVO has been shown to cause more rapid resolution of the edema while achieving a longer-lasting effect.[33]

FUTURE CHALLENGES

The relatively novel treatment modality of tissue-sparing laser therapy combines clinical efficacy with a reduced risk of nontherapeutic iatrogenic side effects. Major challenges in the future of these treatments include clarifying the mechanism of action of subthreshold laser application and fine-tuning the treatment dosimetry. Some investigators have used indocyanine green to help titrate CSR treatment with micropulse,[34,35] and the use of spectral domain OCT and fundus autofluorescence may facilitate monitoring of the disease. It is possible that tissue-sparing therapy using micropulse may permit earlier intervention in conditions such as DME and may be beneficial in improving long-term visual prognosis. Randomized, controlled, prospective clinical trials are needed to help us better understand how to routinely apply this therapy in clinical practice and for the development of stronger evidence-based clinical guidelines. ■

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