

New Frontiers in Selective Retinal Lasers

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ABSTRACT

Retinal laser therapy remains the treatment of choice for proliferative diabetic retinopathy, retinal vascular diseases, and retinal tears. Advances in laser technology have created new treatments that minimize collateral tissue damage while retaining the therapeutic effects of laser therapy. Recent innovations in retinal laser therapy are reviewed, including selective millisecond pulse duration laser, reduced intensity laser therapy, micropulse laser, and selective retinal therapy. These innovations have demonstrated promise in small clinical trials.

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Key words: Laser; Selective retinal therapy; Micropulse laser; Microsecond laser; Retinal wound healing; Photocoagulation

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INTRODUCTION

Retinal laser photocoagulation was first described over 50 years ago and remains the standard of care for many retinal diseases^[1,2].

Conventional retinal laser photocoagulation for diabetic retinopathy, retinal vascular diseases, and retinal tears is typically performed with a continuous wave laser in the green, yellow, or red range, primarily at 514 or 532 nanometers (nm), pulse duration of 100 to 200 milliseconds (ms), spot size from 100 to 500 micrometers (um), and laser power to achieve the clinical endpoint, typically around 100 to 750 milliwatts (mW). Laser therapy is typically empirically titrated to a visible clinical effect of greyish whitening of the retina, which corresponds to photoreceptors necrosis and inner retinal damage.

Although it has proven to be effective clinically^[3-5], adjacent retina is damaged with the laser application, resulting in retinal atrophy and thinning in the regions of laser application, scotomas^[6,7], post-laser lesion enlargement^[8,9], subretinal and choroidal neovascularization^[10], subretinal fibrosis^[11], and progressive visual field loss^[12,13]. These adverse effects of laser can significantly impact a patient's quality of life. These concerns on the destructiveness of laser therapy have led to numerous investigations to provide the same therapeutic effect of lasers with minimizing the side-effect profile, including modulations in pulse duration in the millisecond and microsecond domain, lesion intensity, multiple pulses to allow thermal relaxation, and axial lesion localization, which are discussed below along with clinical results.

INCREASING SELECTIVITY OF MILLISECOND PULSE DURATION LASER

Investigations have been performed using shorter millisecond pulse duration laser ranging from 1 to 100 milliseconds compared to conventional laser^[14]. Shorter millisecond pulse durations resulted in decreased lesion size for an equivalent clinical appearance of the lesion and improved lesion localization but reduced safety window to rupture Bruch's membrane. A pulse duration of 20 ms was found to adequately balance safety with speed. Further modifications have been proposed, including spatial and temporal modulation of laser beams^[15], pattern scanning retinal photocoagulation^[16], and reduced lesion intensity (Figure 1)^[17,18].

Modifications have also been described using OCT to guide more selective focal laser treatment. OCT guided focal laser resulted in

2.5 letters of improved vision ($p=0.04$) and a 45.56 micron reduction in central subfield thickness ($p<0.001$) compared to conventional modified Early Treatment Diabetic Retinopathy Study (mETDRS) focal laser at 1 year^[19]. Further modifications have been described using laser dosimetry to empirically titrate to barely visible burns. The power is reduced from this level and has been shown to result in invisible burns funduscopically but visible on FA and OCT at 50-75% of barely visible level and invisible burns at 30-50% of barely visible level using a software termed Endpoint Management^[20]. A small clinical study of 16 patients with chronic central serous chorioretinopathy of over 4 months duration using 30% of barely visible pulse energy found a gain of 12 letters of vision by 2 months ($p<0.001$) with a decrease in central macular thickness from 350 to 282 ($p=0.004$)^[21]. Subvisible laser burns have been shown to result in upregulation of inflammatory markers after laser application^[22] and improved response to oxidative stress^[23]. The reduced intensity and pulse duration laser has been shown in rabbits to result in retinal lesions in which the photoreceptors fill-in the laser spot within four months (Figure 2)^[24]. This has been shown to result in both restoration of retina structure and function in these laser spots with intact retinal ganglion cells in the laser region through retinal remodeling^[25]. This restoration of morphology has also been shown in humans with OCT following less intense laser burns^[26,27].

MICROPULSE LASER

In contrast to the long exposures and large spots used in TTT, shorter bursts of NIR radiation (810 nm) with small spot sizes (100 to 200 μm) have also been applied for non-damaging retinal phototherapy, termed subvisible diode micropulse (SDM) laser therapy. In this technique, treatment of retinal vascular disease is performed with the express goal of avoiding cellular destruction. Mathematical models of SDM have demonstrated that the hyperthermia in this approach does not exceed the threshold of cell toxicity and has a high degree of selectivity. Low-intensity/high-density SDM allows for complete and confluent (high-density) coverage of the entire diseased retina, such as the areas of macular thickening constituting diabetic macular edema (DME) or ischemic retina with proliferative diabetic retinopathy (PDR). Subthreshold micropulse laser delivers a series

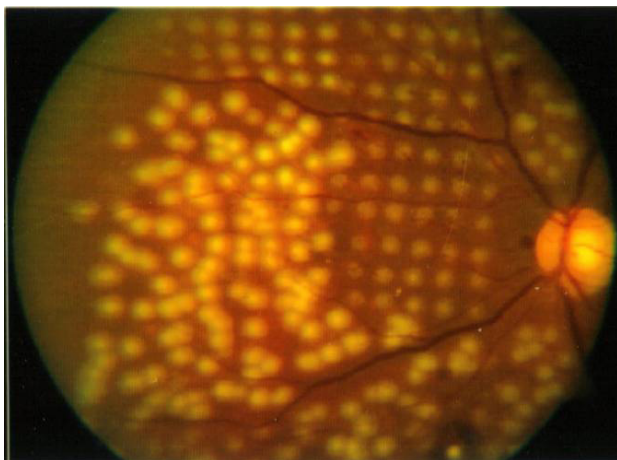


Figure 1 Fundus photograph comparing conventional laser (lower left laser spots in the image) with patterned scanning laser (upper right laser spots in the image, PASCAL, Topcon, Santa Clara, CA, USA) demonstrating more uniformly spaced, smaller, and less intense laser spots with PASCAL.

of short pulses to allow thermal dissipation between each pulse^[28]. Subthreshold laser has been shown in pathologic and histochemical analyses to reduce the changes to the surrounding choroidal and retinal cells^[29].

The micropulse 810 nm diode, low-intensity/high-density subvisible photocoagulator has also been shown to be clinically effective in the treatment of DME and PDR in small clinical series. SDM has been shown to be as effective as modified Early Treatment Diabetic Retinopathy Study (mETDRS) focal laser in the treatment of clinically significant DME. SDM results in improved clinical examination and retinal thickness measurement with optical coherence tomography (OCT) without producing visible retinal damage^[30]. Beneficial effects in the treatment of retinal neovascularization from PDR have also been reported^[31]. These studies, however, are limited by their size and the duration of patient follow-up^[32].

SELECTIVE RETINAL THERAPY WITH MICROSECOND PULSE DURATION LASER

One method to provide retinal phototherapy without severe permanent damage is selective treatment of the retinal pigment epithelium (RPE) by decreasing the laser pulse duration, termed selective retinal therapy (SRT). It has been demonstrated that microsecond (μs) pulse durations that are absorbed by melanin can selectively destroy RPE without damaging the retina^[33,34]. Due to minimal thermal heat diffusion, microsecond and nanosecond laser pulses can produce explosive vaporization of melanosomes, resulting in selective damage to the RPE layer while sparing the photoreceptors and the inner retina. Subsequent RPE proliferation and migration restores RPE continuity. SRT has also been shown to cause a release of inflammatory markers, including matrix metalloproteinases 2 and 9, which may play a role in its treatment efficacy^[35]. Multifocal ERG and histology following SRT has been shown to result in no significant retinal change 30 days after SRT laser application^[36].

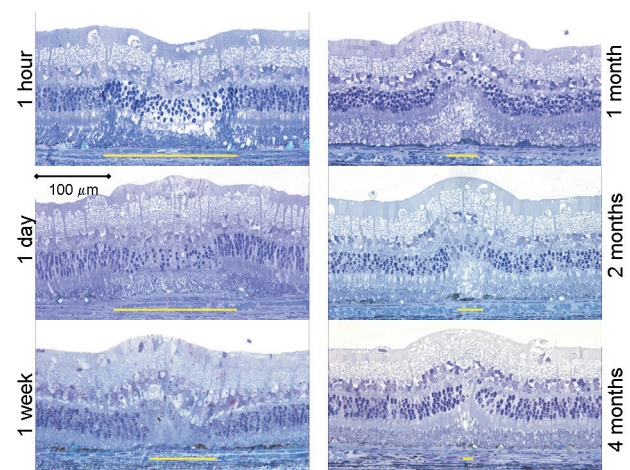


Figure 2 Toluidine blue histopathology of 7ms pulse duration "barely visible" laser burns from 1 hour to 4 months following laser application demonstrating photoreceptor filling in of the damaged area after initial photoreceptor loss in Dutch belted rabbits. A retinal beam diameter of 330 μm and power of 175 mW was used. The yellow bar indicates the extent of damage at the RPE-photoreceptor junction. Gliosis contracts over time in the laser burns with a continuous photoreceptor layer and almost continuous outer retinal morphology by four months. Reproduced with permission from Paulus YM, Jain A, Gariano RF, et al. Healing of retinal photocoagulation lesions. Invest Ophthalmol Vis Sci 2008;49:5540-5545. Copyright 2008 by the Association for Research in Vision and Ophthalmology (ARVO).

The first RPE-selective retinal laser treatment was achieved using 5 μ s argon laser pulses at 514 nm and a repetition rate of 500 Hz^[37]. Currently, several microsecond-pulsed laser systems are available^[38,39]. Recently, an alternative SRT approach has been developed based on a rapidly scanning continuous wave laser, such that RPE cells are exposed to a scanning laser light to achieve dwell times of a few microseconds^[40,41]. This technique has been further refined using an automatic, energy ramping, non-contact, reflectometric dosimetry technique^[42].

Several small clinical studies have demonstrated the efficacy of SRT in diabetic retinopathy, diabetic macular edema, central serous chorioretinopathy, and subfoveal fluid after a rhegmatogenous retinal detachment^[43-46]. A randomized prospective study of 30 patients with chronic central serous chorioretinopathy of at least 3 months' duration with 14 eyes randomized to SRT and 16 eyes as controls found a statistically significant improvement in mean visual acuity with 12.7 letters gained in the laser group versus 6.3 letters gained in the control group ($p=0.04$). SRT also resulted in less subretinal fluid with a decrease of 203 microns in retinal thickness with laser versus 41 microns in control patients at 3 months ($p=0.005$)^[47]. A prospective uncontrolled study of 39 patients with diabetic macular edema found an improvement of 2.4 letters of vision 6 months after laser application ($p=0.02$). 84% of eyes either had stable or improved vision and there were no adverse events associated with SRT^[48].

FUTURE HORIZONS

Advances in laser technology have created new treatments that minimize collateral tissue damage while retaining the therapeutic effects of laser therapy. Thermal damage with conventional laser limits its utility in treating the macula due to tissue damage and scarring. Recently developed improvements minimize or eliminate this side effect. Studies have indicated that laser power approximately half that of barely visible burns produces cellular changes while minimizing tissue injury^[49]. This allows the physician to elicit a therapeutic biological response without causing permanent cell death. Further studies are needed to elucidate the mechanism of cellular response leading to clinical efficacy of laser therapy.

To prove the clinical utility of these new modalities, larger randomized control clinical trials with longer follow-up are required to ensure that these meet or exceed the current clinical standard of care. More clinical trials are also needed of laser treatment in combination with pharmacologic therapy, such as concomitant laser and anti-vascular endothelial growth factor (VEGF) or steroid therapy. We stand on the cusp of a transformation in our care of patients through the use of personalized, targeted therapy and novel laser treatments promise to play an important role in retinal conditions.

CONFLICT OF INTERESTS

The author has no conflicts of interest to declare.

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