

Recent developments in retinal lasers and delivery systems

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Photocoagulation is the standard of care for several ocular disorders and in particular retinal conditions. Technology has offered us newer lasing mediums, wavelengths and delivery systems. Pattern scan laser in proliferative diabetic retinopathy and diabetic macular edema allows laser treatment that is less time consuming and less painful. Now, it is possible to deliver a subthreshold micropulse laser that is above the threshold of biochemical effect but below the threshold of a visible, destructive lesion thereby preventing collateral damage. The advent of solid-state diode yellow laser allows us to treat closer to the fovea, is more effective for vascular structures and offers a more uniform effect in patients with light or irregular fundus pigmentation. Newer retinal photocoagulation options along with their advantages is discussed in this review.

Key words: Diode laser, pattern laser, retinal photocoagulation, subthreshold micropulse laser, yellow laser

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The standard of care for several disorders of the retina is retinal photocoagulation. Over the years there have been changes in lasing mediums, laser delivery systems and wavelengths used. The aim of these new technologies and developments has been to improve patient compliance besides increasing the safety and efficacy of the laser therapy. In the macula, the critical pigments that absorb light and their respective peak absorption spectra are xanthophylls (420-500 nm) within the neurosensory retina, melanin (400-1,000 nm) within the retinal pigment epithelial cells and choroidal melanocytes, and hemoglobin (450-550 nm) within red blood cells, contained within the retinal and choroidal vessels or within areas of extravasated blood.^[1] The familiar "grayish" endpoint of conventional threshold photocoagulation is typically associated with thermal elevations of 20-30°C, which cause coagulation necrosis and characterize the treatment as a supra-threshold photocoagulation. The spreading and decaying thermal wave inevitably reaches the tissues surrounding the burn and this causes the laser burn to expand.

For macular disorders, both green (495-570 nm) and yellow (570-590 nm) wavelengths are suitable as they are well absorbed by melanin and hemoglobin and only minimally by macular xanthophylls. There are very few studies reporting clinical differences between green and yellow laser wavelength in retinal practice.^[2-5] Though none of the studies have reported any large clinical differences related to the wavelength used, the yellow laser may offer some advantages due to its marginally longer wavelength. It is less affected by small-angle

scattering in the transparent ocular media and provides greater transmittance through some corneal or lenticular opacities.^[6] The 577 nm wavelength occurs outside the absorption spectrum of retinal xanthophylls, potentially allowing for treatment close to the fovea.^[7] It also has the highest oxyhaemoglobin to melanin absorption ratio and therefore, is the most effective laser for vascular structures.^[8] The combined absorption by both melanin and oxyhemoglobin of 577 nm causes lesser scatter compared to 532 nm or other yellow wavelengths (561/568 nm). This leads to energy concentration to a smaller volume allowing use of lower powers and shorter pulse durations. High choriocapillaris absorption should also help to provide more uniform effects in patients with light or irregular fundus pigmentation.^[7] It causes less long-term scarring traditionally caused by older lasers and is as effective as currently used lasers but with less side effects. Despite being considered the best wavelength to treat vascular lesions, its application had been limited by the cost and bulkiness of krypton yellow lasers (568.2 nm) and tunable dye lasers (variable wavelength depending on dye). In 2008, the more compact and cost-effective solid-state diode yellow laser (577 nm) was introduced into clinical practice.^[9]

Advances in laser delivery systems have led to a new approach called the sub threshold micropulse mode. It is now possible to deliver a sub threshold laser that is above the threshold of biochemical effect but below the threshold of a visible, destructive lesion, thereby preventing potentially limiting progressive enlargement of laser scars, which can lead to scotoma and loss of color vision.^[10] Subthreshold laser denotes the use of lower energy levels aiming to cause sub-lethal injury to targeted RPE, rather than destroying it and is based on the hypothesis that benefits of photocoagulation are derived from cytokine released by recovering RPE cells.^[11] In the micropulse mode, the laser is delivered in ultra-short pulses (microseconds) that are shorter than the thermal relaxation time of the target tissue. Since, the temperature rise is insufficient to cause ancillary damage to the surrounding retinal tissue it minimizes scarring to the extent that laser spots are generally undetectable on ophthalmic and angiographic examination.^[12]

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The other development in recent times has been the advent of the multi-spot laser delivery systems. By a single foot pedal depression it is possible to deliver laser in a variety of patterns using proprietary software to create adjustable predetermined square arrays, arcs and grids with variable spot sizes and variable distance between spots, all controlled through an intuitive interface.

Pattern scan laser in proliferative diabetic retinopathy and diabetic macular edema

Standard laser photocoagulation is done using single spots with pulse durations of 100 to 200 milliseconds in a continuous mode. The sessions are relatively lengthy and taxing for both patient and surgeon, especially when performing pan retinal photocoagulation. Multispot laser delivers multiple uniform laser burns simultaneously, by a single foot pedal depression in a variety of patterns. These devices save time, streamline patient flow for the retina practice, and reduce discomfort from long laser sessions.^[13,14]

It was inferred from a prospective randomized clinical trial performed to compare efficacy, collateral damage, and convenience of pan retinal photocoagulation for PDR or severe NPDR using 532 nm solid-state green laser (GLX) versus Multispot 532 nm pattern scan laser^[15] that Multispot laser showed lesser collateral damage and similar regression of retinopathy compared with GLX and was less time consuming and less painful.^[16-18]

The Early Treatment of Diabetic Retinopathy Study (ETDRS) established macular photocoagulation as the standard of care for diabetic clinically significant macular edema (CSME). Laser therapy reduced the risk of moderate visual loss secondary to diabetic CSME by 50%, but 12% of the treated patients still lost vision.^[19] The advent of pharmacotherapeutic agents such as steroids and especially, the anti-vascular endothelial factor (VEGF) agents have, in recent years, mitigated the role of lasers in diabetic macular edema.^[20] The collateral damage of tissue, retinal scarring and associated complications of conventional laser, namely, loss of visual acuity, reduction in color, night, and contrast vision, and the rarer, more serious issues of choroidal neovascularization, and epiretinal fibrosis have not helped its cause.

Although the DRCR studies have helped place the anti-VEGF agents in pole position, the repeated number of injections, investigations and hospital visits place too high a burden on the patient and physician alike.^[20] This lack of a "finite therapy" has led to resurgence in interest in novel laser therapies. Subthreshold micropulse laser or tissue-sparing laser photocoagulation has been hailed as an alternative to conventional laser in achieving the beneficial effects of laser while minimizing the harmful effects.

The micropulse laser

A novel laser delivery modality was invented by Pankratov in 1990 wherein the laser energy was delivered in short pulses or "micro pulses" instead of a continuous wave.^[21] It was noted that parameters like retinal spot size, laser energy and duration constant, the size of the ensuing retinal lesion was governed by the duty cycle. The duty cycle is the fraction or percentage of the time span during which the laser energy is emanated compared to the span it is not or the cumulative relaxation time between

pulses. The longer the OFF time between pulses, the lower is the duty cycle leading to reduced tissue heat and damage.

Rationale for subthreshold micropulse laser

Tissue or cellular events occur at far lower laser exposure levels than needed to produce a clinically visible lesion. These may occur at a half to a fourth of the exposure needed to produce ophthalmoscopically obvious lesions. Additionally, VEGF down regulation has been noted to occur at even lower laser exposures. Therapeutic effects may thus be produced with milder retinal irradiances causing lower temperature rises associated with less or no significant retinal damage.^[22,23]

Mainster postulated that as RPE cells were 10-14 μm in height, laser exposures of 0.7 ms or lesser were needed to localize thermal effects within these cells. Manual or automated-pattern conventional photocoagulators have exposures that are at least 50 times longer. There is also the risk that delivering all the laser energy in a single 0.7 ms pulse can induce hemorrhages and post treatment choroidal neovascularization.^[22,23]

In micropulse photocoagulation, laser energy is dispensed in a burst or "envelope" of micropulses, instead of a single pulse. This limits the time for heat conduction to raise the temperature in the adjacent tissue thereby significantly reducing collateral damage. Repetitive micropulses summate to produce the desirable therapeutic effects.^[22,23]

Subthreshold diode micropulse laser for diabetic macular edema

The use of micropulse laser in Diabetic Macular Edema DME was initiated by Friberg and Karatza in 1997.^[24] Luttrell and colleagues in 2005 published, for the first time an account of their experience of using subthreshold MP 810 nm diode laser for DME with complete and contiguous treatment of the entire edematous area without tissue damage.^[25] Micropulse laser has been demonstrated to be as efficacious as the conventional laser.^[26-28]

A study on Japanese DME patients with Subthreshold Diode Micropulse SDM laser using a 15% duty cycle showed that about 95% of the patients maintained or improved vision over 3 m. The power used was 50 to 90% of the threshold burn.^[29]

Vujosevic *et al.*, showed that micropulse laser treatment appears to be as effective as the modified-ETDRS laser photocoagulation for treating DME, but it causes far less damage to the retinal pigment epithelium, as judged by microperimetry and fundus autofluorescence.^[30] Additionally, it was noted that alterations in macular sensitivity may be demonstrable by microperimetry as early as 1 month post-treatment. This may be prior to detection of changes in retinal thickness by optical coherence tomography (OCT).

The technique commonly employed involves primarily performing focal test burns, after which power is reduced by 70% to obtain the ideal "subthreshold" power. This is believed to be the optimal balance between avoiding scarring at any time point post-treatment and yet remaining therapeutic. Hence, SDM laser is an ideal retreatment therapy. With the 810 nm diode as well as the 577 nm yellow laser, an OCT-guided dense treatment pattern or confluent laser applications with overlapping spots is used with a 10 to 15% duty cycle. This

avoids treating only microaneurysms. The entire edematous area is thus treated.

Subthreshold micropulse diode laser for proliferative diabetic retinopathy

The visible end point (conventional) pan retinal photocoagulation remains the primary treatment for proliferative diabetic retinopathy. Despite the effectiveness of conventional photocoagulation, there is no evidence that the inherent retinal destruction in visible end point photocoagulation is actually necessary to achieve a therapeutic benefit in the treatment of retinal vascular disease.^[10,11]

Lutural *et al.*,^[31] performed SDM PRP in 99 eyes of 63 patients with proliferative diabetic retinopathy. All patients were treated with a 500 μ m aerial spot size, 0.20 sec pulse envelope duration, with an initial 2.0 W power setting. Within the laser pulse envelope, a 15% duty cycle, each delivering a train of 100 sequential laser pulses of 300 ms 'on' time separated by 1700 ms 'off' time, was employed for each patient. The median follow-up was 1.0 year (range of 0.3-2.7 years). Treatment sessions per eye ranged from 1 to 6 (with a median of two sessions per eye). The probability of treatment failure end points at 12 m post treatment was 12.5% for vitreous hemorrhage and 14.6% for vitrectomy. Compared to conventional PRP, the response to SDM PRP developed more gradually and without marked contraction of the neovascular tissue. Thus, SDM PRP may be especially useful in the management of eyes with extensive active neovascularization, which are more prone to retinal detachment following conventional PRP. One-third of eyes required a single treatment session, less than the 45% reported for conventional PRP.^[32] Further studies on the safety, efficacy, and optimal treatment parameters of SDM PRP for diabetic retinopathy is warranted.

Subthreshold micropulse laser therapy with yellow (577 nm) laser

The very same micropulse technology used with 810 nm has recently been amalgamated with the new 577 nm lasers, with similar tissue-sparing properties and clinical outcomes, although the evidence is largely anecdotal and disseminated in non-peer reviewed journals. The MP laser therapy protocols employ similar low intensity and high density laser applications in envelopes of repetitive short pulses to induce reduction of the macular edema. Many investigators believe that this may be the safest form of laser for centre-involving DME.^[5]

Thus, a new laser technology has been developed in recent years to minimize effects to the surrounding structures and to minimize photoreceptor injury. The various options combining the benefits of Multi-spot and yellow wavelength include the "Pattern Scan Laser by Optimedica, Santa Clara, CA", the "TxCell Scanning Laser Delivery System, developed by (Iridex Corp., Mountain View, California)", the "MC-500 Vixi Multicolor Scan Laser Photocoagulator (Nidek Co. Ltd.)", and the "Supra scan 577 nm laser delivery system by Quantel systems".

Although anti-VEGF agents have yielded impressive results, subjecting patients with non-centre-involving DME or centre-involving DME without visual loss to multiple injections, however, is fraught with risks. Subthreshold micropulse tissue-sparing laser therapy may be a useful therapeutic modality in these patients.

Micropulse laser in central serous chorioretinopathy

Central serous chorioretinopathy (CSC) is characterized by idiopathic serous detachment of the neurosensory retina secondary to focal defects of the retinal pigment epithelium (RPE). The pathophysiology of CSC has, been thought to involve multiple etiologies and mechanisms that ultimately lead to widespread hyperdynamic and hyperpermeable choroidal circulation.^[33,34]

The conventional laser treatment debrides the RPE at the site of leakage and this in turns leads to the in-growth of the surrounding RPE cells and absorption of the sub retinal fluid. The conventional laser treatment can cause central or paracentral scotoma, contrast sensitivity loss, accidental foveal damage, retinal distortion and choroidal neovascularization (CNV).^[35,36] It is difficult to apply conventional laser if the leak is sub foveal or juxta foveal. Focal laser may close the leak seen on FFA and resolve the sub retinal fluid, but it does not change the amount of choroidal hyperpermeability and leakage, thus the risk of recurrence is not decreased.^[37] Photodynamic therapy (PDT) has also been used to treat focal leaks and chronic CSC associated with diffuse compensation of the RPE, but not without side effects.^[38,39]

Diode and yellow laser micropulse photocoagulation represents a viable modality for the precise control and spatial confinement of laser lesions to the RPE cells. Multiple and overlapping non-visible spots are delivered to the areas of diseased RPE with the aim of stimulating the recovery of the outer blood-retinal barrier.

Lanzetta *et al.*, treated 24 treatment naïve eyes of 22 subjects with the diagnosis of chronic CSC (≥ 3 m), with non-visible micropulse diode infrared laser irradiation. Treatment was delivered with a micropulse diode infrared laser (Iris Medical Oculight SLx). The laser was applied to RPE leaks or zones of RPE decompensation. A continuous wave test spot of 200 μ m and 0.2 seconds exposure time with such power that mild retinal whitening was obtained was placed at the posterior pole. Subsequently, treatment was given with a duty cycle of 15% and the same parameters used for the test spot. Multiple overlapping spots were placed over and adjacent to the area of RPE leak or decompensation. The mean follow-up period was 14 m (range, 3-36 m). One month after laser treatment, nine eyes had complete anatomic resolution of the subretinal fluid in the central macula and seven had incomplete resolution of the exudative detachment, confirmed by OCT.^[40] In another study by Ricci *et al.*, OCT scan revealed complete resolution of the serous neuro-epithelial detachment in five patients and a marked reduction in two patients.^[41]

Chen *et al.*,^[42] treated 26 eyes of 25 patients with persistent CSC and juxtafoveal leakage longer than 4 m' duration with subthreshold diode photocoagulation (SDM). The eyes were divided into 3 groups - focal leakage without associated RPE atrophy (group 1), focal leakage with RPE atrophy (group 2) and diffuse RPE decompensation with indeterminate source leakage (group 3). All patients were followed-up for at least 6 m. In group 1, all patients had total SRF resorption after 1 session of SDM photocoagulation. Eight eyes in group 2 had total SRF resorption after 1 to 3 sessions of SMD laser, whereas 1 patient had persistent SRF. In group 3, only 5 eyes had SRF resorption at the end of the follow-up, and the other 6 eyes

needed photodynamic therapy for final SRF resorption. At the end of the follow-up, the average preoperative foveal thickness was reduced by more than half of its original thickness. A gain of visual acuity of 3 lines or more was achieved in 15 eyes (57.7%) and a gain of between 1 and 3 lines was achieved in 6 eyes (23.1%).

Conclusion

Current data suggest that it is unlikely that there are large clinical differences related to wavelength choice. In the present era of anti-vascular endothelial growth factor agents and with other pharmaceutical products actively under investigation, it is unlikely that an adequately sized randomized clinical trial of different wavelengths will be performed. Treating physicians likely will continue to select the laser wavelength that they have available and are comfortable using.

Conventional laser photocoagulation has been proven to be an effective means to treat ocular diseases. However, it results in full-thickness damage to the RPE, choroid and retina, scotoma formation, choroidal neovascularization, foveal distortion and subretinal fibrosis. Laser photocoagulation is evolving toward laser protocols that can limit and minimize collateral damage.

Subthreshold laser delivery by micropulse technology aims to limit the potential side effects that can develop, while still allowing therapeutic effect. This could therefore be a great advantage when treating eyes with retinopathy of prematurity and other retinal vasculopathies. The main drawback with micropulse subthreshold laser is the absence of a visible end point and the constant worry of under treatment. The ultimate solution, however, should come from a technique that can provide, in real time, the intraoperative monitoring of a pseudo-endpoint with the recording of the locations where such endpoints were achieved. Further studies are needed to clearly establish the potential role of micropulse subthreshold laser therapy in the treatment of various retinal disorders.

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