Short-pulse Laser Treatment: Redefining Retinal Therapy

Minimizing side effects without compromising care.

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Retinal laser photocoagulation was first described 45 years ago and remains the standard of care for many retinal diseases.[1] The Diabetic Retinopathy Study established panretinal photocoagulation as an effective treatment for proliferative diabetic retinopathy.[2] Conventional retinal laser photocoagulation for diabetic retinopathy, retinal vascular applications, and the treatment of retinal breaks is typically performed with a continuous wave laser at 514 or 532 nm with exposure durations from 100 to 200 ms, spot sizes from 100 to 500 µm, and powers from 100 to 750 mW.[3] Thermal ablation of tumors and extrafoveal choroidal neovascular membranes often involve longer pulse durations from 200 to 500 ms and yellow-red wavelengths.[4]

CONVENTIONAL LASER: THE GOLD STANDARD

Although PRP with visible lesions is a highly effective approach to halt angiogenesis, it has numerous side effects, including significant discomfort for many patients,[5] permanent retinal scarring and decreased peripheral, color and night vision.[6,7] Retinal photocoagulation is also effective for treating macular edema, but it causes visible laser scars that can enlarge postoperatively[8-10] and complications that include choroidal neovascularization,[11,12] subretinal fibrosis[13-15] and visual field loss.[16-20] Permanent retinal scarring has multiple detrimental effects: (1) It distorts the normal retinal architecture by replacing it with gliotic/fibrotic matrix; (2) it disrupts normal retinal connectivity; (3) it is associated with an infiltrative/inflammatory process involving cell loss; (4) lack of photoreceptors and/or other retinal cells in the scarring areas directly reduces the visual field sensitivity; and (5) loss of one class of retinal cells may, by trans-synaptic degeneration and by incitement of inflammation, result in loss of other retinal neurons.[21,22]

Ocular neovascular disease results from angiogenic factors produced in response to retinal ischemia. While the exact mechanism is unknown, one theory as to the mechanism of laser treatment is that it reduces neovascular disease by killing retinal cells in the poorly perfused portions of the retina, reducing ischemia and decreasing the production of angiogenic factors.[23-26] Since photoreceptors are the most metabolically active and numerous cells in the retina, PRP for PDR involves the purposeful destruction of a fraction of the photoreceptors.[27]

Systematic clinicopathological analysis of laser-induced retinal lesions over time has demonstrated that exposures of 100 ms and longer typically produce retinal lesions that affect not only the retinal pigment epithelium and photoreceptors, but also the inner nuclear layer, ganglion cell layer and nerve fiber layer.[28]

MINIMALLY TRAUMATIC MILLISECOND LASERS

Recent innovations that have refined these traditional laser parameters to minimize side effects while retaining the therapeutic effect include modulations in pulse duration, lesion intensity and lesion localization, and use of photosensitizing agents. Each innovation is discussed below.

Pulse Duration

The semiautomated pattern-scanning retinal photocoagulation system PASCAL (PAttern SCAn Laser; OptiMedica Corp., Santa Clara, CA) has been recently introduced, which allows for patterns of four to 56 burns to be applied in less than one second, using a scanning laser with shorter

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pulse durations.[29] This delivery system allows for the creation of well-aligned arrays of retinal lesions in a shorter time (**Figure 1**).

Investigations of retinal photocoagulation have found that 10- to 20-ms exposures can produce retinal lesions of all clinical grades, if power is increased accordingly. In addition, shorter pulse durations result in improved lesion localization, as compared to conventional 100 ms exposures.[30]

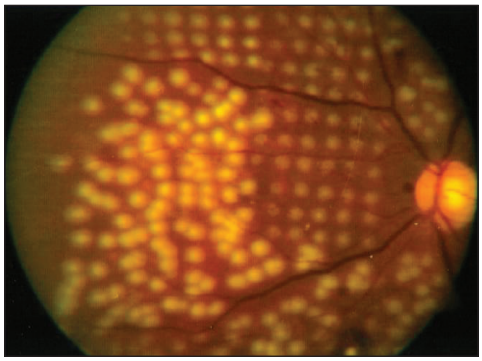

Figure 1. Comparison of conventional laser application (at left and below) and PASCAL (on the right) in a rabbit eye.

Several small pilot clinical studies have been undertaken, comparing photocoagulation performed with 10- to 20-ms pulses to conventional 100-ms exposures. All studies have found that 10- to 20-ms pulse duration lesions to result in similar clinical endpoints. A study by Sanghvi et al. performed 10- to 20-ms pulse duration photocoagulation in 75 eyes in 60 patients and found it to be safe and effective.[31] In a study by Al-Hussainy et al, 20 patients were treated with a conventional laser (100 ms, 180 mW) and short-pulse duration (20 ms, 500 mW), each lesion type in half of every treated retina. Patients were asked at the end to rate the pain of each of the two treatments from 0 (no pain) to 10 (the worst pain ever experienced). Conventional PRP resulted in a pain score of 5.11, whereas short-pulse duration had a much lower pain score of 1.4.[32]

Additional studies have also confirmed that shorter-duration laser burns cause less perceived pain in patients than conventional laser lesions.[33] A study by Muqit et al. evaluated the evolution of the lesions produced by 10- and 20-ms pulse duration using ophthalmoscopy, Fourier domain optical coherence tomography and fundus autofluorescence in 17 eyes of 11 patients. Short-pulse duration lesions localized to the outer retina and RPE and showed more predictable lesion characteristics at 18 months post-treatment.[34]

One limitation to these studies, however, is their small sample sizes. All of these trials occurred in small cohorts of patients with fewer than 100 treated eyes. While the preliminary results with 10- to 20-ms pulse duration lesions look encouraging in terms of their rapidity of application, reduced perceived patient pain and improved lesion localization, larger multicenter, randomized, controlled trials and longer patient follow-up are needed for definitive comparison of the clinical efficacy of shorter-pulse duration treatment with conventional therapy.

Lesion Intensity

In conventional retinal photocoagulation, the typical endpoint of laser treatment is an ophthalmoscopically visible grayish-white lesion that develops due to thermal denaturation and coagulation of the retina. The heat is predominantly deposited in the RPE and pigmented choroid but spreads by diffusion and causes irreversible damage to the photoreceptor outer and inner segments.[35,36] However, recent evidence has suggested that retinal lesions might not be permanent in smaller, less intense burns and that the outer retina can fill the damaged areas in animal models, including rats, rabbits and snakes (**Figure 2**).[37-39] It is important to keep in mind that less intense lesions with the same spot size are often smaller, and thus a larger number of lighter lesions is required to maintain the same clinical efficacy.

Several reports regarding light PRP, also referred to as minimum intensity photocoagulation (MIP),[40,41] and subvisible treatment using micropulse photocoagulation[42,43] have indicated that these approaches may have an equivalent efficacy to conventional PRP in causing regression of high-risk PDR. In addition, small studies find that MIP is associated with fewer complications and fewer treatment sessions. At 12 months, light PRP was reported to be equivalent to classic PRP in reduction/elimination of diabetic macular edema, visual improvement, change in contrast sensitivity and decreased foveal retinal thickness on OCT.[44] Both of these approaches offer the therapeutic benefit of conventional therapy without many of its detrimental side effects.

Lesion Localization

The Early Treatment Diabetic Retinopathy Study (ETDRS) established grid photocoagulation as an effective therapy for clinically significant DME.[45] Comparison of the modified ETDRS with a mild macular grid (MMG) found the modified ETDRS grid photocoagulation to be superior to MMG.[46] Focal laser coagulation also has additional applications in treating CNV associated with myopic degeneration.

Response to laser therapy has also been shown to depend on subclassification of the condition. OCT can be used to subclassify diabetic macular edema into four categories: diffuse retinal thickening (DRT), cystoid macular edema (CME), serous retinal detachment, and vitreomacular interface abnormalities (VMIA). In a study of 70 eyes from 45 patients who underwent focal laser photocoagulation with different subcategories of DME, patients with DRT were found to achieve a greater reduction in retinal thickness and greater improvement in visual acuity than patients with CME or VMIA.[47]

Laser application can also be modulated through the intravenous administration of photosensitizers such as verteporfin (Visudyne, Novartis/QLT) with concomitant

administration of low-intensity laser. The photosensitizer activation results in the formation of reactive oxygen, primarily singlet oxygen ($^1O_2$),[48] and direct cellular injury, such as vascular endothelial cell injury and vessel thrombosis, while preserving the surrounding retina, RPE and choroid. Multicenter, randomized clinical trials (the TAP and VIP studies) have established PDT with verteporfin as an effective therapy to reduce visual acuity loss in patients with CNV in age-related macular degeneration.[49,50]

Side effects of PDT with verteporfin include photosensitivity reactions, dye extravasation, transient visual disturbances and infusion-related back pain. However, PDT has decreased in popularity in recent years due to the efficacy of anti-VEGF agents in halting and reversing vision loss with CNV. Selectivity has also been demonstrated using laser-activated gold nanoparticles to selectively target retinal vascular endothelial cells for treatment of CNV.[51]

The selective treatment of drusen in patients with AMD using conventional photocoagulation caused reduction in the number of drusen. However, this did not result in visual acuity improvement, and it increased the incidence of CNV. Thus, it is not advised.[52,53]

MICROSECOND PULSE DURATION: SELECTIVE RETINAL THERAPY

While conventional photocoagulation has applications in many retinal diseases, it has limited use in macular treatment due to scarring, which results in significant central visual scotomas. Many diseases involving the macula, such as AMD, DME, geographic atrophy and CSR, are thought to be caused by dysfunction of RPE cells. This hypothesis suggests a need for RPE-specific treatments that would allow for macular therapy in these conditions.

The RPE plays an important role in photocoagulation by housing the pigment melanin, which absorbs much of the laser energy.[54] Mathematical models and empiric data have demonstrated that microsecond pulse durations can selectively destroy RPE cells without damaging the retina.[55,56]

This has led to the development of selective retina therapy (SRT): microsecond laser exposures that target RPE cells without affecting the photoreceptors, neural retina or choroid. The first RPE-selective retinal laser treatment was achieved using 5-µs argon laser pulses at 514 nm and a repetition rate of 500 Hz in rabbit eyes.[57] It has been shown that the application of microsecond pulses at the thermal relaxation time of melanosomes in the RPE (1 µs) leads to the formation of microbubbles and selective RPE cell death, while the surrounding retinal temperature remains sublethal.[58] This allows for selective RPE treatment while avoiding photoreceptor damage.

Currently, several microsecond-pulsed laser systems have been developed.[59,60] Recently, an alternative approach to SRT has been developed: application of a rapidly scanning continuous wave laser such that the RPE cells are exposed to laser light during several microseconds.[61]

In 2000, the first clinical study reported the efficacy of SRT in 12 patients with diabetic maculopathy, 10 patients with soft drusen and four with CSR.[62] SRT was performed with an Nd:YLF laser (wavelength of 527 nm) using a pulse duration of 1.7 µs, and patients were examined by ophthalmoscopy, fluorescein angiography, indocyanine green angiography and infrared imaging. The number of hard exudates, drusen and serous detachment improved after treatment in patients with diabetes, soft drusen and CSR, respectively. No visual loss (photoreceptors) after treatment was confirmed by microperimetry.

Similarly, microsecond pulse-duration laser therapy has been shown to be both safe and effective in small trials in

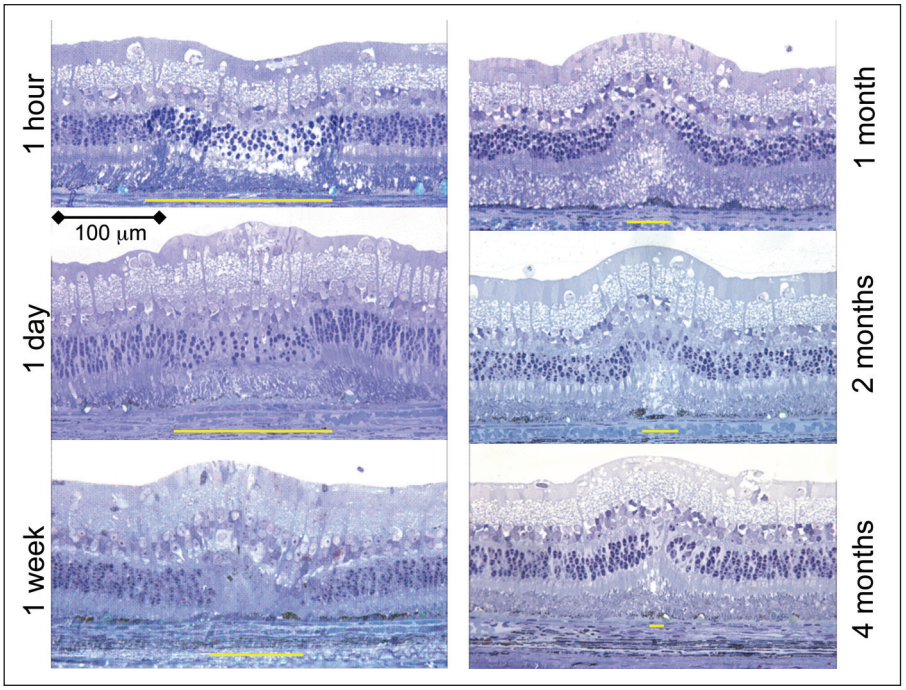

IMAGE FROM PAULUS YM, JAIN A, GARIANO RF, ET AL. HEALING OF RETINAL PHOTOCOAGULATION LESIONS. *INVEST OPHTHALMOL VIS SCI*. VOLUME 49, NUMBER 12, PP. 5540-5545. COPYRIGHT 2008 BY ARVO.

Figure 2. Histology of short (7 ms), less intense pulse duration over four months showing retinal filling in of the damaged area. Demonstrates toluidine blue histology of "barely visible" laser lesions produced with a pulse duration of 7 ms, a retinal beam size of 330 µm, and a laser power of 175 mW in rabbits. The yellow bar indicates the extent of damage at the RPE-photoreceptor junction. Lesions exhibit localization of the damage to photoreceptors. Gliotic replacement of the damaged photoreceptors continues to contract over time, reaching almost continuous appearance of the outer retina with normal morphology at four months.

applications such as CSR[63] and subfoveal fluid after rhegmatogenous retinal detachment.[64] SRT is currently being investigated for its utility in treating drusen, CSR, CNV and branch retinal vein occlusion. Preliminary results from an international multicenter trial have been reported to be quite promising among 60 patients with diabetic maculopathy and 10 patients with CSR.[65]

Near-infrared laser (810 nm) operating with bursts of submillisecond pulses has been applied for more gentle coagulation (OcuLight SL; Iridex Corporation, Mountain View, CA). This wavelength is selected due to its reduced absorption by photoreceptors and hemoglobin — and thus its more selective absorption by melanin in RPE and pigmented choroid. Typically, a sequence of micropulses of 100 µs in duration separated by 50-150 µs is applied during 200 to 500 ms. This micropulse system has been shown to be clinically effective in small trials for the treatment of macular edema from venous occlusion and diabetic retinopathy.[66]

THE FUTURE OF LASERS IN RETINAL TREATMENT

While pharmacologic therapies such as VEGF inhibitors and corticosteroids have proved to be effective in the treatment of macular diseases such as AMD, recent advances in laser technology have created new modalities that result in minimal tissue damage while retaining the therapeutic effects of laser therapy. Thermal diffusion in conventional 100-ms laser systems limited their utility in treating the macula due to scarring, resulting in central visual scotomas. The recently developed improvements minimize or eliminate this side effect and thus allow for safe macular laser therapy.

In addition to continuing to be the gold standard of therapy in several retinal conditions, laser can also be used concurrently with pharmaceutical treatments such as corticosteroids or VEGF inhibitors. Improved understanding of the mechanism of laser therapy, an area of active investigations, may lead to further enhancements of laser treatments.

One of the mechanisms by which retinal photocoagulation is thought to produce therapeutic benefit in vascular retinal disease is destruction of retinal cells in the poorly perfused portions of the retina, thus limiting the ischemia and decreasing the production of angiogenic factors.[24-27] Since photoreceptors are metabolically the most active and numerous cells in the retina, PRP involves the purposeful destruction of a fraction of the photoreceptors to reduce the retinal oxygen demand.[67]

Recent experiments looking at rat models of hypoxia have found that photoreceptors act as a repository of growth factors in hypoxic conditions that cause the angiogenesis and increased vascular permeability characteristic of these conditions.[68] These findings suggest that selective destruction of photoreceptors, while sparing the inner retina, should not only increase availability of oxygen, but also reduce the angiogenic and permeability factors.

Further improvements in laser systems have been recently demonstrated at the Association for Research in Vision and Ophthalmology 2009 conference that might become available clinically in the coming years. These include optoacoustic monitoring of retinal temperature in real time to achieve real-time automatic dosimetry for more reproducible homogenous photocoagulation lesions.[69] In addition, retinal-navigated laser photocoagulation using eye tracking and registered diagnostic imaging with scanning slit ophthalmoscope allows one to register FA and other imaging data to better guide photocoagulation delivery.[70] This technology will allow for better targeting of the areas with pathology, identified by OCT, FA and other imaging modalities.

CONCLUSION

Continuous innovations in laser technology and progress in the understanding of retinal pathology make us believe that improvements in the treatment of retinal diseases using laser therapy will continue in the years to come. **RP**

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