

Advances in Retinal Laser Therapy

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ABSTRACT

Since the 1960s, laser therapies have played a critical role in the treatment of numerous retinal diseases. Significant advances have been made in laser technology and the molecular understanding of laser-tissue interactions over the past 55 years to maximize the therapeutic effect while minimizing side-effects. While pharmacologic therapies (e.g., anti-vascular endothelial growth factor or anti-VEGF) are playing a larger role, laser therapy remains an important treatment modality for proliferative diabetic retinopathy (PDR), diabetic macular edema (DME), sickle cell retinopathy, retinal vein occlusions, central serous chorioretinopathy, tumors,

polypoidal choroidal vasculopathy, and retinal tears. With the development new laser technologies such as selective retinal therapy, subthreshold micropulse laser, nanosecond laser, photomediated ultrasound therapy, and navigated laser, the risk of adverse events has been significantly reduced. This review summarizes the latest developments in retinal laser therapy.

Key words: Laser photocoagulation; Retina; Selective retinal therapy; Subthreshold micropulse laser; Nanosecond pulse laser; Photo-mediated ultrasound therapy; Navigated laser

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INTRODUCTION

Laser photocoagulation has been widely used to treat many ocular diseases for over 55 years. This method uses light to coagulate targeted tissue and achieve therapeutic effects^[1]. Numerous research and clinical trials have proven its efficacy, particularly in retinal vascular disorders such as diabetic retinopathy, retinal vein occlusions, and choroidal neovascularization. Retinal laser therapy often utilizes 514 nm continuous wave (CW) argon or frequency doubled 532 nm neodymium-doped yttrium aluminum garnet (Nd: YAG) solid-state lasers with pulse durations in excess of 50 milliseconds. However, safety is always a major concern of such laser treatment. It is reported that conventional laser therapy can cause adverse events such as enlarged retinal scars, subretinal fibrosis, decreased peripheral vision, decreased night vision, choroidal neovascularization, and reduced macular sensitivity^[2-5]. Also, the efficacy of pharmacologic agents can sometimes surpass that of laser photocoagulation^[6,7]. Moreover, it is reported that conventional laser can cause a transient up-regulation of vascular endothelial growth factor (VEGF) in the neurosensory retina, retinal pigment epithelium (RPE), and choroid in mice that may be responsible for decreased visual acuity due to PRP (panretinal photocoagulation) induced macular edema^[8,9].

Despite these disadvantages, laser photocoagulation still has several advantages and remains an important therapy. Laser is cheaper and less invasive than anti-VEGF intravitreal injections. In addition, laser therapy often requires significantly fewer patient visits,

which can be particularly important in resource limited settings and developing countries where patients and family members travel a day to see a physician and cannot do this every 4 weeks. Laser therapy does not have the potential systemic cardiovascular side-effects, such as stroke, along with local risks such as endophthalmitis, cataract, and retinal tear or detachment. Also, laser photocoagulation can still be an important choice when other treatments demonstrate minimal effect or as combination therapy. Furthermore, laser parameters such as wavelength, power, spot size, and pulse duration can be altered to reduce the side effects of laser and even improve the outcome. In order to achieve such goals, new technologies like subthreshold micropulse laser, nanosecond pulse duration laser, photo-mediated ultrasound therapy, and navigated laser have been developed recently. The aim of this review is to discuss these new technologies and future perspectives.

SELECTIVE RETINAL THERAPY

Conventional retinal photocoagulation laser therapy is thought to induce its therapeutic effect by targeting metabolically active photoreceptors, thereby decreasing the hypoxic drive and VEGF production^[10,11]. After photocoagulation, pigment-epithelium-derived factor (PEDF) is reported to be upregulated, which can inhibit retinal and choroidal neovascularization by inducing apoptosis in activated vascular endothelial cells^[12]. Also, it is reported that after the RPE is destroyed by the absorbed heat, a wound healing process starts. Then, RPE cells proliferate and migrate into the lesion site^[13,14]. This process may provide a physical window through which oxygen may diffuse without being consumed by photoreceptors, thus increasing oxygen tension in the retina^[15].

Selective retinal therapy (SRT) was described to limit the induced damage to RPE and thus eliminate or reduce the risk of laser-induced adverse events caused by thermal damage to the surrounding tissue, particularly the neurosensory retina^[16]. By decreasing the pulse duration of the laser to the microsecond regime, thermal effects to photoreceptors are minimized and the effect is noted at the RPE. Histologic analysis reveals that the damage in SRT lesions is primarily limited to the retinal pigment epithelium (RPE). Transient changes are noted in the outer segments of the photoreceptors that likely reflect their interdigitations with the RPE, but there is no permanent damage to the neurosensory retina that is noted^[17].

Despite of these advantages, SRT laser treatment still has certain limitations. One important limitation is the difficulty in determining the appropriate laser dose for each irradiation session because the lesion is invisible. Also, the melanin concentration varies approximately 50%, even within the same retina^[18]. Since the core mechanism of SRT is microbubble formation, a real-time feedback measurement technique able to detect microbubbles is the most effective solution. Fortunately, techniques like opto-acoustic (OA) and optical-feedback techniques (OFT) can assist with this situation^[19]. OA is a non-invasive device able to determine the temperature rise in real-time during photocoagulation by repetitively exciting thermoelastic pressure with nanosecond probe laser pulses and has been demonstrated in small clinical trials^[19]. A corresponding automatic control system called temperature controlled photocoagulation (TCP) was also successfully used in rabbits. It is reported that the TCP can facilitate uniform retinal lesions over a wide power range^[20]. The OFT is also an automatic system that can detect backscattered light generated by microbubbles and stop irradiation when a certain threshold is reached^[21]. It is demonstrated that SRT with OFT could selectively target the RPE without damaging the neurosensory retina^[17].

SUBTHRESHOLD MICROPULSE LASER

Previously, investigators have reported effective treatment of diabetic macular edema with low-intensity laser therapy^[22]. Later, a technology called subthreshold diode micropulse (SDM) photocoagulation was introduced that applied micropulse 810-nm diode laser. Small clinical studies have demonstrated that SDM is effective for the treatment of DME and proliferative diabetic retinopathy without causing any adverse treatment effects or complications^[23-25]. In order to further reduce the adverse effects in the neurosensory retina, a new technique called subthreshold micropulse laser was introduced. This short duration laser can still change the metabolic activity and gene expression of the retinal pigment epithelium, which has also been demonstrated at the histologic level^[26, 27]. Also, it has been reported that short pulse duration laser induces fewer inflammatory cytokines in the neurosensory retina compared with conventional pulse duration laser. The levels of VEGF, interleukin 6 (IL-6), regulated upon activation normal T-cell expressed and secreted (RANTES), and monocyte chemotactic protein 1 (MCP-1) is significantly up-regulated after conventional laser treatment compared with short pulse laser, which may prevent macular edema caused by panretinal photocoagulation^[28]. By decreasing the duty cycle of the laser, the laser energy is divided into numerous short repetitive pulses typically from 100 to 300 μ s with 1700-1900 μ s between each pulse in a total laser envelope of 200 to 300 milliseconds. As a result, the duty cycle of the laser can be decreased to as low as 5%-10% of the conventional laser so the tissue can have time to release the heat accumulated in each laser pulse. The effective laser energy can be as low as 10% of the threshold and thus caused no damage to neurosensory retina (Figure 1)^[29,30]. However, the mechanism of RPE destruction is also completely different in this case. Roeder's study demonstrated that microsecond pulses can induce intracellular microbubbles around the melanosomes, which leads to selective damage of RPE cells^[31].

Subthreshold micropulse laser has been investigated in some small clinical trials in clinical applications including diabetic macular edema, branch retinal vein occlusion, and central serous chorioretinopathy (CSCR). It is reported that patients with diabetic macular edema can get equal or even better visual acuity as well as better preservation of electrophysiologic function after micropulse laser treatment compared with conventional laser therapy^[30,32]. The same results can also be observed in other diseases. Patients with macular edema due to retinal vein occlusion got an improvement in both visual and anatomical outcomes, and patients suffering from CSCR observed a resolution of subretinal fluid^[6,33]. During the follow-up period, the laser spot is barely recognizable even with fluorescein angiography or autofluorescence imaging.

NANOSECOND LASER

The idea of micropulse laser motivated the development of nanosecond laser, which delivers approximately 0.2% of the energy per pulse compared with conventional laser. In this case, the duty cycle is even shorter. Brinkmann *et al* demonstrated that the mechanism of nanosecond laser induced RPE cell damage is the formation of transient microbubbles around melanosomes after the boiling temperature of the intracellular plasma, which is similar to micropulse laser^[34]. A research comparing the energy needed by 3-nanosecond pulse laser and CW argon laser to cause RPE damage found that the killing threshold of 3-nanosecond laser is between 36 mJ/cm² to 89 mJ/cm², while the CW laser is 10346 mJ/cm²^[35]. Low level of laser energy can prevent thermal injury to surrounding

tissue. Some pilot trials have demonstrated a favorable outcome of nanosecond laser therapy compared with conventional laser for treating diabetic macular edema^[36]. Also, patients with age-related macular degeneration (ARMD) had a 44% reduction in drusen area in the treated eye and 22% in the fellow eye. However, visual acuity did not improve within the 12-months follow-up period (Figure 2)^[37]. It has been demonstrated that nanosecond laser can restore the expression of MMP-2, MMP-3 (matrix metalloproteinases) as well as several extracellular matrix (ECM) genes, including collagen, laminin and components of elastic fibers, and several integrin subunits. This occurs not only in the treated eye, but also in the fellow eye. The increase in these proteins may improve attachment of the overlying RPE to Bruch's membrane (BM), inhibit the RPE detachment, and slow the atrophic process in ARMD^[38].

PHOTO-MEDIATED ULTRASOUND THERAPY (PUT)

Recently, our group developed a novel, selective, non-invasive technique using synchronized ultrasound bursts and nanosecond laser irradiation called photo-mediated ultrasound therapy (PUT). With the help of HIFU (high-intensity focused ultrasound), the laser energy level can be further decreased. PUT takes advantage of the high native optical contrast among biological tissues and has been demonstrated to treat microvessels without causing collateral damage to the surrounding tissue^[39]. By changing the wavelength of the laser beam, PUT can selectively target different tissue. The mechanism behind PUT is also microbubble formation. PUT has demonstrated significant promise in pre-clinical animal models including rabbits and has significant potential for clinical translation in the near future.

NAVIGATED LASER TREATMENT

Conventional laser, particularly panretinal laser photocoagulation, can take a long time and can be painful to patients and fatiguing to physicians. The introduction of pattern scanning laser systems such as PASCAL (Topcon Medical Laser Systems, Inc.; Tokyo, Japan) allow delivery of various predetermined laser spot patterns that significantly reduce treatment time and the patient's perception of pain. However, a reduction of pulse duration to 10-30ms is needed to deliver an array of laser spots within the eye fixation time^[40-43]. This reduction in pulse duration results in burns of a decreased spot size and thus necessitates more treatment spots to be placed in an eye. The under-treatment due to insufficient laser treatment may be responsible for the decreased efficacy that has been reported in some clinical trials.

Photography-based navigated laser photocoagulation with retinal eye tracking (NAVILAS; OD-OS GmbH, Berlin, Germany) has also been introduced. This system has the ability to decide the laser treatment spots with image guidance before treatment, and then the laser beam is precisely delivered to the predetermined treatment pattern with continuous monitoring of eye movement, which allows for a prolonged pulse duration. NAVILAS has been successfully used in both focal and panretinal treatment and also as a part of combined therapy^[44-47]. With the help of such navigated technology, laser photocoagulation can be more accurate and effective but also less painful to patients^[48].

CONCLUSION

Lasers play a critical role in the management of diseases of the vitreous, retina, and choroid. Retinal laser therapy has significantly

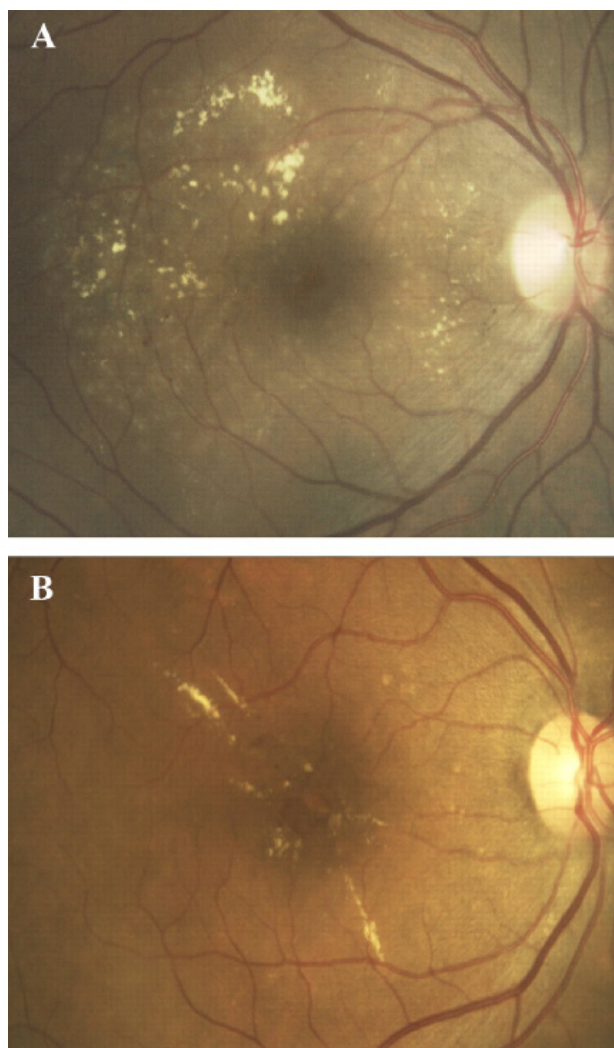


Figure 1 (A) Fundus color photography of the barely visible mETDRS burn endpoint immediately after treatment. (B) Fundus color photography of an HD-SDM nonvisible endpoint immediately after treatment. From: Randomized Clinical Trial Evaluating mETDRS versus Normal or High-Density Micropulse Photocoagulation for Diabetic Macular Edema Invest. Ophthalmol. Vis. Sci., 2011; 52(7): 4314-4323. doi:10.1167/iovs.10-6828

advanced for more than 55 years since it was first described in 1961. Improved understanding of laser-tissue interactions and more selective laser techniques have optimized clinical outcomes while reducing side effects and collateral tissue damage. Selective and shorter pulse duration retinal therapy can significantly reduce the laser energy required while optimizing the therapeutic effect on targeted tissue. The mechanism of some ultrashort pulse duration laser is microbubble formation, and thus other techniques such as HIFU can be used to enhance it and reduce the required laser energy further, such as with photo-mediated ultrasound therapy. With the development of these new technologies, retinal laser therapy has become more efficient and effective with less pain and adverse events. Continuing innovations in laser technology and progress in understanding laser-tissue interactions make us believe that laser therapy will continue to play a critical role in treating retinal disease for many years to come.

DISCLOSURES

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Nanosecond-laser application in intermediate AMD: 12-month results of fundus appearance and macular function

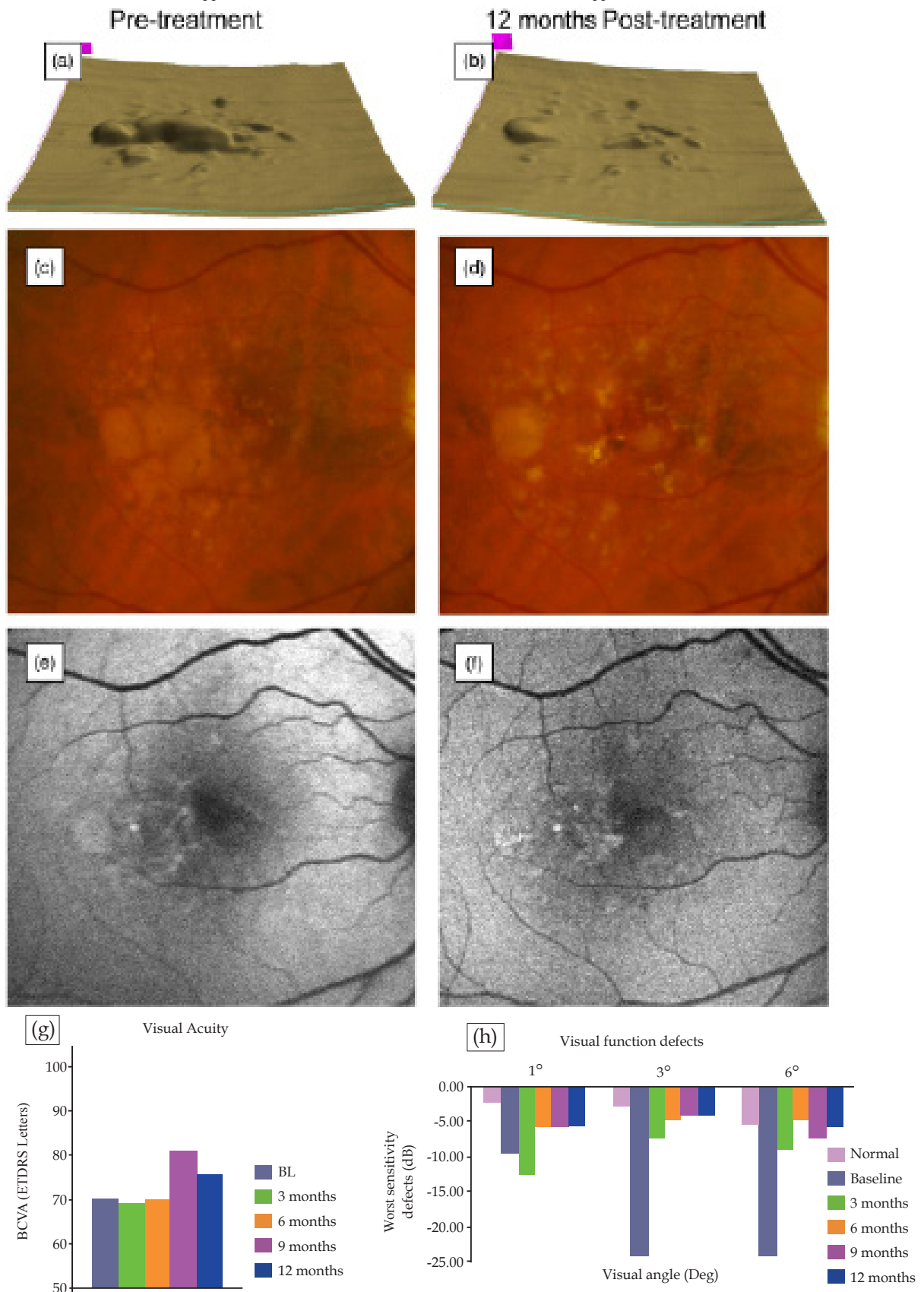


Figure 2. Pre-treatment (left side) and 12-month post-treatment (right side) physical and function changes in the treated eye (OD) in a 72-year-old participant using laser protocol 1. From top (a,b) retinal pigment epithelium (RPE) layer maps from spectral domain optical coherence tomography (OCT), (c,d) fundus photos, (e,f) auto-fluorescence (FAF) images, (g) visual acuity (VA) changes and (h) visual function changes at the points of worse visual sensitivity defect. Note the reduction in para-foveal drusen and hyper-fluorescence on the FAF image and the improvement in both VA and flicker sensitivity, especially at the worst location of the 3° ring. From: Clinical & Experimental Ophthalmology Volume 42, Issue 5, pages 466-479, 11 NOV 2013 DOI: 10.1111/ceo.12247 <http://onlinelibrary.wiley.com/doi/10.1111/ceo.12247/full#ceo12247-fig-0005>.

(YMP). YMP is party on a patent on photo-mediated ultrasound therapy (PUT) through the University of Kansas. All research was performed in accordance with the Declaration of Helsinki and all local, regional, and national law.

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