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REVIEW

A Review of Subthreshold Micropulse Laser and Recent Advances in Retinal Laser Technology

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ABSTRACT

The role of retinal photocoagulation as a first line therapy for various retinal pathologies has decreased with the introduction of anti-vascular endothelial growth factor therapy. However, retinal laser therapy remains an important treatment modality, especially with the emergence of micropulse subthreshold treatment and the integration of newer technology such as augmented reality and semi-automated delivery. This review summarizes current evidence for micropulse laser as a treatment modality and discusses the role of new technology such as augmented reality in the future of laser therapy.

Keywords: Augmented reality; Micropulse; Navigated laser; Photocoagulation; Image-guided therapy; Retina; Subthreshold

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INTRODUCTION

Laser photocoagulation has been in use for the last several decades to treat various retinal disorders, including proliferative diabetic retinopathy (PDR), diabetic macular edema (DME), macular edema associated with retinal vein occlusion (RVO), central serous chorioretinopathy (CSC) and choroidal neovascularization (CNV). Its efficacy and safety have been studied extensively in several landmark studies published in the 1980s [1–5]. However, with the advent of anti-vascular endothelial growth factor (VEGF) therapy and its success in the treatment of various retinal pathologies, the utilization of conventional thermal photocoagulation has declined.

Whether there is still a role for laser therapy for these entities in the anti-VEGF era and if so, to what capacity, are questions that are being asked more frequently. In this paper we will review the potential role of micropulse laser as an adjunct and the evidence for its efficacy in the treatment of common retinal pathologies. In addition, we discuss recent innovations, specifically augmented reality technology and automated laser delivery capabilities and their role in the future of laser retinal therapy.

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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MICROPULSE LASER

Conventional laser therapy is thought to induce its therapeutic effect by targeting metabolically active photoreceptors, thereby decreasing the hypoxic drive and VEGF production. In terms of focal laser for the treatment of macular edema, direct laser photocoagulation of microaneurysms is thought to be the mechanism of action [6, 7]. However, there is increasing evidence that the retinal pigment epithelium (RPE), after heat stimulation by a nearby laser burn, is ultimately responsible for modulating the exudative response [8]. Furthermore, subthreshold laser therapy, a term used to describe the deliverance of laser energy below the threshold of causing permanent tissue destruction, has been shown to alter the metabolic activity and gene expression of the RPE, resulting in the release of growth factors and cytokines that regulate angiogenesis and vascular leakage [9–11]. These changes in protein expression of the RPE by subthreshold laser have also been demonstrated on a histologic level [12].

Laser parameters such as wavelength, power, spot size and pulse duration, can be altered in order to decrease the amount of thermal energy delivered to limit permanent tissue damage. Micropulse laser has emerged as the main modality to achieve subthreshold treatment where a visible laser burn is not detectable, even with fluorescein angiography or autofluorescence imaging. Micropulse laser achieves this subthreshold application by decreasing the "duty cycle" of the laser. Instead of one single continuous pulse, the laser energy is divided into numerous short repetitive pulses typically from 100 to 300 μs with 1700–1900 μs in between each pulse. This effectively decreases the "duty cycle" of the laser to as low as 5%–10% of the conventional laser. By having extended periods of rest in between each laser micropulse, the retinal tissue is able to disperse the accumulated heat to avoid the threshold of apoptosis and cell death. Micropulse power as low as 10% of the threshold power has been demonstrated to result in localized changes in the RPE while sparing the neurosensory retina

on light and electron microscopy [13]. There are currently several commercially available micropulse laser systems: Quantel Medical (Cedex, France) 577 nm; IRIDEX (Mountain View, CA) 532 and 577 nm; and OD-OS (Berlin, Germany) 577 nm. There is emerging evidence that micropulse laser may be as effective as conventional laser photocoagulation in the treatment of various retinal pathologies, the most pertinent of which will be reviewed.

Diabetic Macular Edema

Micropulse laser has been shown in several randomized control trials to be as or more effective than conventional focal laser photocoagulation in the treatment of DME [14–16]. In these studies, visual acuity was found to be either equivalent or superior in the micropulse laser group when compared with the conventional focal laser group at 1 year. A study with long-term follow-up demonstrated sustained visual and anatomic improvement at 3 years [17]. In addition, several groups have shown better preservation of electrophysical function with micropulse laser as revealed by either multifocal electroretinogram or microperimetry [18, 19]. There have been no studies comparing micropulse laser to anti-VEGF, which is currently the treatment of choice. However, focal laser may have an important role in DME refractive to anti-VEGF or non-fovea-involving DME, especially in light of the effectiveness of subthreshold tissue-sparing laser therapy.

Macular Edema Secondary to Retinal Vein Occlusion

Currently, studies of micropulse laser for the treatment of macular edema due to RVOs have been very limited. Parodi et al. published the only randomized control trial comparing the effect of micropulse laser in this entity with conventional threshold laser therapy and found no difference between the two groups in terms of vision and resolution of edema at 2 years [20]. The same group of investigators recently compared micropulse laser to intravitreal

bevacizumab for the treatment of macular edema secondary to RVO recurring after conventional laser therapy and found bevacizumab to be superior in both visual and anatomical outcomes at 1-year follow-up [21]. Currently, the role of micropulse laser in this group of patients appears to be limited.

Central Serous Chorioretinopathy

Subretinal fluid accumulation in CSC is thought to be secondary to a combination of choroidal hyperpermeability and RPE dysfunction. The majority of cases resolve spontaneously but treatment of recurrent and chronic disease can be challenging. Existing treatment modalities include conventional laser photocoagulation and photodynamic therapy (PDT). Secondary choroidal neovascularization and subretinal scarring can result from chronic untreated CSC or from conventional laser therapy. Micropulse laser has been shown in several studies to result in resolution of subretinal fluid [22–25]. However, these studies either lacked a control group or were limited in the size of the study.

Proliferative Diabetic Retinopathy

Currently evidence for the efficacy of micropulse laser for the treatment of proliferative diabetic retinopathy is limited. There is one published report on subthreshold micropulse laser as an alternative to conventional panretinal photocoagulation to date [26]. In the study ninety-nine eyes were treated with micropulse laser, and, at 1-year follow up, 12.5% developed vitreous hemorrhage and 14.6% underwent vitrectomy. The authors concluded that this was similar to previously published reports on outcomes with conventional panretinal photocoagulation. However, the analysis included thirty-five eyes with severe non-proliferative diabetic retinopathy. Furthermore, the study was limited by an uncontrolled design, relatively small sample size, and short follow- up.

As opposed to entities like DME and CSC where the pathophysiology involves RPE dysfunction, for which micropulse laser may be able to stimulate resorption of fluid even with subthreshold energies, proliferative diabetic retinopathy may involve a different pathophysiology. The major hypothesis in proliferative diabetic retinopathy involves angiogenic stimulus from ischemic retina, the destruction of which leads to decreased angiogenic stimulus and improved oxygenation of the remaining non-ischemic retina [27]. Further studies including randomized control trials of micropulse laser in proliferative diabetic retinopathy are needed.

As anti-VEGF therapy become the first-line therapy in various retinal diseases, the routine use of conventional macular laser has declined significantly. However, in difficult cases that are refractive to anti-VEGF therapy or in cases with significant treatment burden from continuous injections, focal laser is still an important treatment modality. Subthreshold micropulse laser is a less invasive alternative to conventional laser photocoagulation that has been shown to be as or more effective in the treatment of DME without causing permanent tissue damage [14–16]. Its role in the treatment of other retinal diseases is yet to be determined. Future randomized control trials are required to better understand how this modality can be applied with more clearly defined clinical guidelines.

AUGMENTED REALITY

Augmented reality is the integration of computer-generated information with the user's environment in real time. It uses the existing environment and overlays useful information on top of it. An everyday example is the ten-yard line that is ubiquitous when watching an American football match on television. The yellow line, which is not physically present on the field and is only seen by the television audience, marks the location of the first down marker. Augmented reality has many useful applications in medicine. Examples range from the projection of a patient's vein over the skin in preparation for obtaining intravenous access to the overlay of previously acquired 3-D images

onto the surgical field to label important anatomical landmarks.

Navigated laser therapy is an example of augmented reality in the field of retinal laser therapy. It utilizes an eye-tracking laser delivery system with the ability to overlay infrared, fluorescein angiography, and optical coherence tomography images onto the real time-fundus image. Registered image overlays allow the surgeon to map and target precise treatment areas while the eye-tracking system compensates for patient movement. In addition, preset grid patterns with equidistant spacing can be delivered semi-automatically to the planned treatment area with precision. Navigated laser therapy has been shown to significantly increase the accuracy of laser delivery with greater than 95% of laser spots delivered within 100 microns of the desired target [28, 29]. This is particularly important when targeting microaneurysms in the treatment of DME. Accurate laser delivery contributes to the efficacy of navigated laser delivery [30, 31]. In addition, two studies have demonstrated a reduced treatment burden with anti-VEGF therapy when combined with navigated laser therapy [32, 33]. Furthermore, subthreshold micropulse mode is integrated into the commercially available navigated laser platform with documentation of treatment spots. This is critical when planning for repeat treatments because previously treated areas are invisible with micropulse laser.

CONCLUSION

The role of retinal photocoagulation as a first line therapy for various retinal pathologies has largely been replaced with anti-VEGF since its introduction. However, despite the emergence of anti-VEGF, retinal laser therapy still has an important role in the treatment of many diseases and is a useful modality in a retina specialist's armamentarium. Recent advances such as micropulse subthreshold laser, which has been demonstrated to be especially effective in DME, will be utilized more widely as results from randomized controlled clinical trials are made available. Furthermore, the future of retinal laser therapy will include wider adoption of augmented reality such as navigated laser to assist surgeons in more accurate treatments with semi-automated delivery.

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