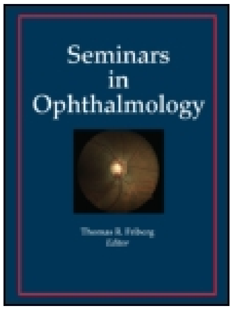

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REVIEW

Subthreshold Diode Micropulse Laser: A Review

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ABSTRACT

The subthreshold diode micropulse laser is a form of non-damaging thermal laser therapy which has shown efficacy in multiple retinal conditions. The purpose of this article is to review the use of subthreshold diode micropulse laser as an emerging treatment modality for the treatment of retinal disease. The proposed mechanisms of action, safety, efficacy, recommended laser treatment parameters, and clinical applications for which the use of subthreshold diode micropulse laser has been studied will be reviewed.

Keywords: Minimum-intensity, non-damaging, photocoagulation, subvisible

INTRODUCTION

The advent of retinal laser photocoagulation in the 1960s spurred a revolution in the field of ophthalmology and the management of retinal disease. In the 1980s, there were numerous landmark studies establishing the efficacy of laser photocoagulation for previously untreatable retinal conditions, including proliferative diabetic retinopathy (PDR), diabetic macular edema (DME), choroidal neovascularization (CNV) in age-related macular degeneration (AMD), central serous chorioretinopathy (CSCR), and cystoid macular edema (CME) associated with retinal vein occlusion (RVO).[1–7]

Though conventional laser photocoagulation is effective, it causes permanent retinal damage. Recent advances in laser technology have focused on maximizing the therapeutic benefits of thermal laser while minimizing retinal damage. Of these emerging subthreshold laser modalities, subthreshold diode micropulse laser has been the focus in most of the current literature and will be the focus of this review. Alternative subthreshold treatment methods will be reviewed in brief.

MATERIALS AND METHODS

Candidate articles were identified through a comprehensive literature search of PubMed, using the terms "subthreshold diode micropulse laser," "micropulse laser," "subvisible laser," "subthreshold laser," "non-damaging laser," "minimum-intensity photocoagulation," "phototherapy," and "photostimulation."

RESULTS

Proposed Mechanism of Action of Thermal Laser

The exact mechanism accounting for the success of photocoagulation has remained controversial, though its effectiveness is well-established.[1–7] Interestingly, the underlying pathophysiology of retinal diseases responsive to laser photocoagulation is heterogeneous. Early theories postulated that direct laser photocoagulation of abnormal blood vessels (microaneurysms, neovascular tissue) induced regression of these pathologic vessels. In opposition to this theory, it is well-established that there is regression of macular edema when microaneuryms are not directly treated (i.e., macular grid laser) and that retinal neovascular fronds regress after panretinal photocoagulation (PRP) without directly treating the new blood vessels. Other theories postulate that hypoxia is the primary underlying pathologic mechanism of retinal vascular disease and that the oxygen-consuming photoreceptor cells are the primary therapeutic targets for laser

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photocoagulation. Others have suggested that the laser scars themselves allow more oxygen from the choriocapillaris to diffuse to the inner retina and relieve inner retinal hypoxia.

Through translational research, we have developed a more sophisticated understanding of the therapeutic mechanism of laser treatments. It is our current understanding that the target of thermal laser is neither the abnormal blood vessels nor the oxygen-demanding photoreceptors, but rather the underlying retinal pigment epithelium (RPE). Numerous studies have shown that retinal laser photocoagulation stimulates expression of various metabolic, biochemical, and structural changes at the level of the RPE, which modify the exudative response. Biologic activity can only be generated from viable cells, and not from cells that have undergone apoptosis (burned area). This therapeutic response is now thought to arise from the tissue adjacent to a retinal burn, where the RPE is exposed to sublethal doses of thermal energy.

Conventional Laser Photocoagulation

In conventional photocoagulation, laser energy passes through the transparent preretinal and retinal structures before it is absorbed by melanin in the RPE, producing heat. Excessive RPE temperature spreads heat by conduction to adjacent tissues, causing thermal damage and denaturation of the proteins in the neurosensory retina (coagulation). This appears ophthalmoscopically as a visible burn. The collateral damage sustained by the RPE and surrounding tissues is proportional to the laser intensity or duration during which supratheshold hyperthermia is sustained. With increased laser intensities, lateral spread of thermal energy to the surrounding RPE causes damage beyond the confines of the laser spot diameter (enlarged scars). Similarly, anterior heat diffusion into the retina can cause damage to the inner retina and nerve fiber layer (arcuate defects) and posterior diffusion into the choroid, causing activation of choroidal pain receptors and iatrogenic breaks in Bruch's membrane (hemorrhage, subsequent CNV).

Reduced-Intensity Laser Photocoagulation Techniques

In order to minimize these deleterious effects of focal laser treatments, retina specialists have advocated the use of less destructive photocoagulation techniques, particularly when treating near the macula. The modified Early Treatment of Diabetic Retinopathy Study (mETDRS) laser protocol was developed after a survey of retina specialists showed consensus that, in practice, less laser energy can be used while maintaining similar outcomes and avoiding the delayed expansion of laser scars.[8] The treatment parameters used in this mETDRS protocol include a smaller spot size (50 μm) and lower power level (50–100 ms) to create light grey or barely visible burns (2 burn-width spacing).

In 2006, the Patterned SCAnning Laser (PASCAL) was introduced in an effort to further reduce the intensity of photocoagulation, minimize retinal damage, and mitigate pain. The PASCAL method takes advantage of a shorter pulse duration (10–30 ms) to minimize heat diffusion in treated areas.[9]

Minimal-Intensity, Non-Damaging, Subthreshold Laser Therapy

The proposed mechanism of action of a non-damaging laser is induction of RPE hyperthermia below the threshold for cell death. Numerous studies have shown that a thermal laser has a stimulating effect on RPE metabolism and regeneration through one of several mechanisms. Photocoagulation has been shown to stimulate metabolic activity and gene expression at the level of the RPE, and the subsequent release of growth factors, enzymes, and cytokines, which regulate angiogenesis and vascular leakage (vascular endothelial growth factor (VEGF), pigment epithelium-derived factor (PEDF), transforming growth factor beta2 (TGF-β2), stromal cell-derived factor1 (SDF-1), and matrix metalloproteinases (MMPs)).[10,11–15] Other studies have shown that subthreshold laser energy induces local regenerative effects, such as restoration of the RPE blood retinal barrier and increased cell adhesion.[16,17] More recent data have supported the role of heat shock protein expression in response to the cellular stress of sublethal thermal injury. Heat shock proteins are ubiquitous molecules which are produced in response to stress and help repair damaged tissue and create "thermotolerance," increasing the threshold at which cell damage and apoptosis occur from thermal, inflammatory, oxidative, or hypoxic injury.[18,19] Sramek et al. have shown that the energy required to stimulate heat shock protein expression is significantly lower than the energy required to cause apoptosis or a visible laser burn.[18] An effective subvisible laser relies on the proper titration of laser parameters to achieve energy levels that are high enough to "stress" the RPE cells and produce a biochemical response without causing permanent cell damage.

With this knowledge, a new era of laser therapy has recently emerged where various strategies have been implemented in an attempt to minimize laser intensity to levels that stimulate the RPE, but do not cause permanent or visible retinal damage. The overarching concept is referred to as subthreshold or subvisible laser. Unlike conventional lasers, the advantage of the subthreshold laser is that treatment is virtually painless and non-damaging. Large areas of the retina can be treated confluently, the fovea can be directly treated, and treatment can be repeated without detectable structural or functional damage.

Current Subthreshold Laser Treatment Modalities

The *subthreshold diode micropulse (SDM)* laser as a non-damaging treatment modality was first described in 1990.[20–22] This method employs the use of multiple repetitive micropulses of energy (typically 100–300 microseconds in duration) delivered in a burst, or ''envelope'' (typically 100–500 ms total envelope duration). Therefore, the laser is not continuous, but is ''ON'' only for microseconds at a time and ''OFF'' in between pulses, allowing the tissue to cool between each micropulse. Subthreshold treatment can be achieved when the duration of micropulse exposure is shorter than the time needed for the thermal wave to propagate to adjacent tissues. The exposure duration is controlled by the duty cycle, or percent of time the laser is in the ''ON'' mode during the envelope. Typically, instantaneous power settings for micropulse (MP) laser delivery are higher than those needed for the equivalent continuous wave (CW) laser mode. The laser power is typically titrated based on a test spot in CW mode to create a barely visible or threshold burn, and then switched over to MP mode with a short duty cycle (5–15%) and increased power (100–400%), with the endpoint being an ophthalmoscopically invisible ''burn.''[23] Micropulse lasers have been used in the treatment of a wide range of retinal disease in clinical studies and are commercially available and FDA-approved.

Transpupillary thermotherapy (TTT) was one of the earliest subthreshold laser modalities and has been used in the treatment of CNV, CSCR, and intraocular tumors. This low-irradiance strategy implements a very large spot size and long duration to spread the total laser energy both spatially and temporally, so that no single cell is exposed to suprathreshold intensities at any point in time.[24] In practice, it is difficult to properly titrate this laser and the heat distribution tends to be non-uniform within the large spot size. This occasionally leads to severe retinal damage and vision loss.[25] For this reason, TTT is used infrequently in practice.

The *conventional continuous wave (CW) laser* can also be delivered at lower power to achieve subthreshold treatment, though the therapeutic window when using the conventional 100 ms exposure duration is narrow.[10,18,26] It is difficult to effectively titrate a conventional laser without over- (iatrogenic retinal burns) or undertreating (no therapeutic effect).

Selective retinal therapy (SRT) is an emerging technique which is similar to micropulse laser, but uses even shorter micropulses (1–5 μs) of green laser delivered at a constant frequency (typically 500 Hz), and total energy is titrated to subthreshold doses. Very high peak temperatures are delivered to a localized area, causing explosive vaporization and selective destruction of the RPE without collateral damage. Adjacent RPE cells proliferate and migrate to repair the transient localized defect.[27,28] There is limited literature on the clinical efficacy of SRT, but early studies have shown potential efficacy in diabetic macular edema and central serous chorioretinopathy.[29,30] SRT is not currently available commercially.

Photothermal therapy (PTT) or subvisible photostimulation is a new subthreshold laser delivery method that uses short pulses (15 ms) of continuous-wave yellow lasers.[31] Prior to initiating clinical trials, optimal laser parameters were established through extensive preclinical investigation, including computational tissue modeling integrating data from histologic studies (light microscopy, transmission and scanning electron microscopy), biochemical analyses, and multimodal imaging studies (optical coherence tomography [OCT], fluorescein angiography [FA]). This laser is commercially available as a patterned scanning laser with software that adjusts the laser energy (power and duration) to user-specified levels (typically 30% threshold). The retina is treated confluently using a 200 ms spot and 0.25 spacing. Using this method, Lavinsky et al. found that consistent subvisible laser treatment could be achieved while remaining both supratherapeutic and sublethal. Results from an initial interventional case series using photothermal therapy in chronic central serous chorioretinopathy have shown promise, and further upcoming clinical trials for CSCR, DME, and AMD are planned.[32]

Subthreshold Micropulse Diode Laser: Safety and Efficacy

Studies have shown that a conventional grid laser causes immediate and permanent damage to the retina and surrounding structures. In-vivo studies have demonstrated a loss of the RPE and photoreceptor layers after focal laser treatment, corresponding to the location of visible retinal burns.[33] Damage can be seen on OCT as ellipsoid disruption and hyperreflective outer retinal changes consistent with early inflammation and late glial proliferation and on FA as hyperfluorescent window defects.[34] In contrast, the subthreshold diode micropulse laser has been shown to treat the RPE selectively without neurosensory or RPE destruction in histopathologic studies.[12] Using a 10% duty cycle results in localized changes in the RPE layer without any neurosensory retinal changes.

There are no detectable RPE or retinal changes when a 5% duty cycle is used. Eyes treated with SDM laser typically have no detectable changes on fluorescein angiography, fundus autofluorescence, or OCT.[34–37] Inagaki et al. showed that 100% of eyes treated with conventional CW laser developed immediate outer retinal changes on OCT which were persistent in 62%, whereas no changes in OCT morphology were seen in eyes treated with SDM laser.[34] Despite the absence of any apparent structural retinal damage, the ability to visualize treated areas may be possible with specialized techniques.[38]

It is well-described that conventional focal laser photocoagulation causes functional deficits such as decreased central visual acuity and scotomas. In contrast, no functional damage is detected with psychophysical testing after subthreshold diode micropulse laser. Vujosevic et al. compared microperimetry in 50 subjects randomized to SDM or modified ETDRS laser and found that the mean central 4-degree and 12-degree retinal sensitivity increased significantly in the micropulse diode laser group and decreased significantly in the mETDRS group, despite similar improvements in macular edema.[36] Venkatesh et al. used multifocal ERG to compare conventional and subtheshold lasers. In this study, signal voids were detected in only 20% of subjects treated with subthreshold lasers and in 80% of eyes treated with conventional lasers.[39] Both groups had similar resolution of macular edema on OCT. They concluded that the micropulse laser is as effective as the conventional laser with better preservation of electrophysiological function.

CLINICAL APPLICATIONS OF SUBTHRESHOLD DIODE MICROPULSE LASER

Diabetic Macular Edema: High-Quality Evidence of Efficacy

Firberg and Karatza first described the use of a micropulse diode laser for DME in 1997.[40] Since then, there have been several, well-designed prospective randomized clinical trials (RCT), all consistently showing that the subthreshold micropulse diode laser is as or more effective than conventional macular grid photocoagulation in the treatment of diabetic macular edema.

In 2004, Laursen et al. performed the first prospective RCT comparing the efficacy of subthreshold micropulse diode (810 nm) to conventional Argon (512 nm) laser in 23 eyes.[41] Best-corrected visual acuity (BCVA) remained stable and was comparable in both groups. Interestingly, OCT thickness improved in patients who received subthreshold, but not conventional laser treatment. In this study, the micropulse laser was delivered in an atypical manner, using significantly longer envelope duration than typically recommended or used in the majority of other studies. It is unclear whether this accounted for the greater anatomical success.

Figuiera et al. performed a similar study in 2009, where they randomized 84 eyes to SDM vs. conventional argon laser.[42] Eyes were treated at baseline and then again at four months if edema persisted. They found no difference in best-corrected visual acuity, contrast sensitivity, or central retinal thickness between the two treatment groups at 12 months. They reported that laser scars were visible in 59% of eyes treated with conventional mETDRS argon laser and in 14% of eyes treated with subthreshold diode micropulse laser. They concluded that the treatments were equally effective in treating DME, with less scarring in the micropulse diode group. Despite the use of seemingly typical mETDRS and SDM laser settings, there was a higher incidence of visible burns in the ‘‘subthreshold’’ group than is expected for subthreshold laser treatment, where the typical endpoint is an ophthalmoscopically invisible burn, and a lower incidence of visible burns in the conventional argon laser group than expected (typically 100%). This may suggest that the laser parameters used in this study lead to overtreatment in the subthreshold group and undertreatment in the mETDRS group to some degree.

Another randomized trial in 2011 by Lavinsky et al. compared mEDTRS focal laser ($n = 42$) to normal-density (ND-SDM; $n = 39$) or high-density (HD-SDM; $n = 42$) subthreshold diode micropulse laser in patients with DME and visual acuity in the 20/40–20/400 range.[43] They hypothesized that, because of the less damaging effect of the subthreshold laser, treating a confluent and therefore greater area of the RPE may have a superior RPE-stimulating effect than conventional grid spacing designed for threshold applications. The HD-SDM treatment consisted of confluent laser spots, and the ND-SDM conformed to the typical grid pattern used for mETDRS treatment (two ‘‘burn’’-widths apart). Subjects were treated at baseline and then pro re nata at three- and six-month visits if edema persisted and the subject had decreased vision, increased OCT thickness, or leakage on FA. They found that high-density MP laser was associated with a significantly greater improvement in visual acuity at one year on average compared to the mETDRS group, as well as a greater number of subjects gaining three lines of vision and smaller number losing three lines of vision. Changes in OCT thickness were similar between the two treatment groups. There was no significant change in BCVA or OCT thickness in subjects treated with normal-density subthreshold laser (no effect). They concluded that high-density SDM was superior to mETDRS photocoagulation and that selection of proper laser parameters is essential in producing a therapeutic effect.

Two additional groups reported results from randomized controlled studies comparing the subthreshold micropulse diode laser to conventional modified ETDRS laser, but also included electro- and psychophysical indices in addition to visual acuity and OCT outcomes.[35,39] Both studies had similar outcomes to previous studies showing no difference between conventional and micropulse lasers in terms of resolution of macular edema or change in visual acuity. In addition, Venkatesh et al. showed that subjects treated with a micropulse laser had significantly fewer detectable signal voids (4/23) compared with subjects treated with a conventional laser (18/23), and concluded that the micropulse diode laser was superior to the conventional focal laser due to better preservation of electrophysical function.[39] Vujosevic et al. showed that, despite similarities in visual acuity and anatomic outcomes, there was a significant benefit of micropulse over conventional laser in terms of visual function.[35] Using microperimetry, they showed that the mean central retinal sensitivity increased in the micropulse group and decreased in the mETDRS group.

There have also been numerous uncontrolled, prospective, interventional case series and retrospective studies, all of which provide an overwhelming preponderance of support for the use of SDM laser in diabetic macular edema.[44–49]

One study with long-tem follow-up showed that vision improved or stabilized in 84% of subjects in the first year and this was maintained over a three-year follow-up.[45] They also showed significant anatomic improvements (decreased DME in 92% and complete resolution in 88%), and that these results were maintained in the long term. The majority (72%) of patients required retreatment with a mean of two total treatments required over the three-year follow-up period.

Another interventional case series included 33 subjects who were previously treated with conventional argon macular grid laser, in addition to 187 treatment-naïve subjects.[46] They found a significant improvement in OCT thickness in both the primary and secondary treatment groups and improvement or stability in visual acuity in 85% of the treatment-naïve subjects and 65% of the group previously treated with conventional argon laser.

The preponderance of the evidence suggests that the subthreshold diode micropulse laser has similar efficacy to the conventional ETDRS focal laser without damaging the retina. Most of these studies were designed prior to the anti-VEGF era. There are no studies to date comparing the efficacy of SDM laser to pharmacologic therapy, which is the current preferred treatment in center-involving diabetic macular edema.[50–53]

Macular Edema in Retinal Vein Occlusion: Moderate-Quality Evidence of Efficacy

To date, there has been a single, small, randomized controlled trial evaluating the efficacy of the subthreshold micropulse diode laser to the conventional threshold grid laser for macular edema in RVO.[54] This was before the results of the BRAVO study revealed the superiority of Ranibizumab to a focal grid laser.[55] Parodi et al. included subjects with BCVA <20/40 who met criteria for treatment according to previous studies. They found similar efficacy in both treatment groups, both in terms of visual acuity gains and resolution of macular edema. Both treatments were associated with a two-line improvement in BCVA after one year. At the conclusion of the study (two-year follow-up), the mean foveal thickness was similarly reduced in both treatment groups. Resolution of edema, however, was first seen at six months in subjects receiving threshold treatment and was delayed (12 months) in the subthreshold micropulse laser group.

Several other preliminary studies have consistently demonstrated a significant but delayed treatment effect of subthreshold micropulse lasers on macular edema in subjects with retinal vein occlusion, but the aforementioned visual acuity benefit has not been replicated.[54,56,57] There is limited literature on the topic, but the majority of the studies claim that the micropulse laser has no visual acuity benefit in these subjects.[56–58] There are limited data on the natural history of macula edema in branch retinal artery occlusion, but evidence suggests that macular edema resolves in 20–40% of patients with BRVO without any treatment over 18–21 months, so it is unclear whether subthreshold MP laser has any benefit over observation, given that the preponderance of data suggests that the benefits/improvements are delayed and simply anatomic.[5,59,60]

One small, randomized interventional study showed inferiority when comparing micropulse laser to intravitreal bevacizumab in patients who had been previously treated with conventional laser.[58] They found no improvement in BCVA or macular edema in the MP laser group as compared with significant improvement in both measures in the anti-VEGF group. There have not been any studies to date comparing the efficacy of MP laser to anti-VEGF injections in treatment-naïve patients.

Despite underwhelming evidence of the efficacy of subthreshold laser as a primary treatment for RVO, several investigators have sought novel uses for subthreshold lasers in RVO. One study investigated the utility of subtheshold micropulse lasers in patients with very good visual acuity (>20/40), for whom no current treatment is generally recommended.[57] They found that, in subjects with chronic macular edema (>6 months) and VA >20/40, there was no visual acuity benefit despite resolution of edema. Other investigators postulated that the delayed effects of the micropulse laser might be augmented by the relatively rapidly acting triamcinolone. They compared the efficacy of subtreshold micropulse lasers alone or in combination with intravitreal triamcinolone and found no functional improvement in the laser monotherapy group compared to the group also receiving intravitreal steroids. They concluded that the micropulse laser may be beneficial when combined with triamcinolone, but there were no data to support that combination therapy had any benefit over triamcinolone alone.

The micropulse laser is associated with a delayed but consistent anatomic effect on macular edema in RVO, though the preponderance of evidence suggests no visual benefit. Limited data from two small studies suggest that the micropulse laser is most likely inferior to pharmacotherapy (triamcinolone or bevacizumab).

Central Serous Chorioretinopathy: Low-Quality Evidence of Efficacy

The pathophysiology of central serous chorioretinopathy (CSCR) is distinct from that of macular edema. Subretinal fluid accumulation in CSCR has been proposed to be secondary to a combination of choroidal vascular hyperpermeability and RPE decompensation. Photodynamic therapy (PDT) targets abnormal choroidal blood vessels and works by counteracting choroidal vascular hyperpermeabulity, whereas laser (thermal) treatment may decrease leakage in CSCR by positively affecting the tight junctions and RPE pump though the upregulation of biologic factors of treated RPE.[61] It is difficult to prove a definitive treatment effect when the natural history of the disease is typically a self-limited process. For this reason, nonrandomized uncontrolled studies are of limited benefit, and large, randomized controlled trials are necessary to substantiate efficacy of any treatment over observation alone.

For subthreshold micropulse lasers in CSCR, there are only two prospective controlled studies: one pilot study, which was not randomized, and another study where treated subjects were not well-matched with controls. Koss et al. reported results from a small, nonrandomized controlled interventional study, where subjects choose their own treatment (micropulse laser, intravitreal bevacizumab, or observation), and found that subjects treated with lasers had better outcomes, both functionally and anatomically, compared to either bevacizumab-treated or observed subjects.[62] There were significant differences in BCVA and perceived metamorphopsia with MP laser treatment as well as greater incidence of SRF resolution on OCT. The subjects treated with subthreshold lasers also had less incidence leakage on fluorescein angiography after treatment (12%) compared to either the intravitreal bevacizumab (60%) or observation (92%).

In another small, randomized pilot trial, 15 patients with chonic CSCR (>6 months) were randomized to micropulse ($n=10$) or sham laser ($n=5$).[63] Subjects were retreated every three months pro re nata, and the sham group was eligible to crossover if subretinal fluid persisted after three months. The results of this study are difficult to interpret because treated subjects were not well-matched with controls. The sham group had much more chronic disease, worse visual acuity, greater incidence of juxtafoveal leakage—all factors suggesting a worse prognosis than SDM-treated subjects. They noted that the mean BCVA improvement was 2.5 lines in the treatment group versus no improvement in the sham group at three months. All five sham subjects crossed over during the course of the study; there were subsequently significant improvements in BCVA and macular thickness during the treatment phase compared to the sham phase of the study. Despite the limitations of this study, they concluded that SDM laser may be associated with resolution of SRF and leakage from chronic CSCR as well as significant functional improvements.

There are a number of other interventional case series showing complete resolution of subretinal fluid ranging between 55–71% of patients treated with subthreshold micropulse diode laser and at least partial resolution (improvement) in 75–100% of patients over 2–14 months' follow-up.[64–67] However, without proper controls, it is not clear that laser treatment alters the natural course of the disease.

Age-Related Macular Degeneration: Low-Quality Evidence of Efficacy

Because the subthreshold thermal laser has the ability to repair damaged RPE, investigators have also explored applications in age-related macular degeneration. Several large trials in the 2000s investigated the efficacy of the subthreshold laser in early AMD and consistently found that laser induced drusen regression, but did not improve outcomes, and in one large study even increased the risk of developing choroidal neovascularization.[26,68,69] The study was stopped prematurely and they concluded that the use of subthreshold laser was not recommended.[26] The subthreshold laser used in these studies was not micropulsed. The exposure duration was decreased by 50% after determining threshold power, and it is not clear that the parameters were within the therapeutic range. The authors noted that ''subthreshold'' laser spots, even though ophthalmoscopically invisible, were apparent on fluorescein angiography, suggesting supratherapeutic effect.[26] There is interest in replicating these studies using a micropulsed laser with more controlled parameters.[70]

There is one case report of successful anatomical resolution of a serous pigment epithelial detachment (PED) and improvement in BCVA from 20/40 to 20/20 after subthreshold micropulse laser.[71] This patient had non-neovascular AMD with drusen and a large chronic pigment epithelial detachment that showed no leakage on FA or associated subretinal fluid on OCT. Results from this study have not been further investigated in the literature.

There has been one retrospective review of 19 eyes with retinal-choroidal anastomoses associated with advanced age-related macular degeneration treated with micropulsed laser.[72] In this study, they achieved complete closure in 43% and complete resolution of SRF in 53%. Additionally, 100% were found to have a reduction in flow on high-speed ICG (partial closure) compared to baseline. Now that we have good treatment options for choroidal neovascularization, we rarely see the late-stage complications of long-standing untreated CNV and disciform scars which tend to lead to retinal-choroidal anastomoses.

Recently, another retrospective study investigated the efficacy of the micropulse laser as a resensitizing treatment in patients with wet AMD unresponsive to anti-VEGF therapy.[19] Thirteen patients were included who showed persistent leakage on FA or fluid on OCT after multiple monthly anti-VEGF injections, including a failed trial of three monthly aflibercept injections. They were treated with subthreshold micropulse laser before resuming aflibercept injections. The authors reported significant anatomical improvement after rechallenge with aflibercept following a single session of SDM laser, though there is no lasting visual benefit.

There are several ongoing studies investigating other applications of micropulse lasers in AMD, including geographic atrophy, in which a dysfunctional RPE is thought to be fundamental in its pathogenesis.[73]

Proliferative Diabetic Retinopathy: Low-Quality Evidence of Efficacy

Unlike exudative choroidal and retinal disease processes, the pathogenesis of neovascularization in proliferative diabetic retinopathy is still mostly conceptualized as an ischemic process where aberrant blood vessels form at the borders of ischemic and perfused retinal tissue. In this way, ablating the abnormal nonperfused retina is thought to be essential in the mechanism of neovascular regression in PDR. This seems to be a definitive treatment in most cases, assuming that there is stability of the underlying disease. It is accepted that there are other biologic mechanisms involved, such as VEGF, and intravitreal injections of anti-VEGF seem to be temporizing, even in the absence of tissue ablation. Therefore, it is possible that the micropulse laser could have a similar temporizing effect on proliferative disease in diabetic retinopathy.

There is a single report on micropulse laser panretinal photocoagulation for proliferative diabetic retinopathy.[74] This was a retrospective, single-center, single-investigator study, where 63 patients (99 eyes) were offered subthreshold micropulse laser as an alternative to conventional PRP. The intended benefit was to increase the comfort of the procedure. The study was limited by an uncontrolled design. No patient chose conventional PRP for comparison. The authors reported that the incidence of new vitreous hemorrhage after subthreshold PRP was 12.5% over one year. Additionally, of those who had vitreous hemorrhage at baseline or developed a hemorrhage during follow-up, the probability of requiring vitrectomy at one year was 14.6%. They concluded that this was comparable to previous reports of the incidence of vitreous hemorrhage and vitrectomy after conventional argon PRP, but these groups cannot be directly compared.[75]

Laser Parameters

One of the challenges in the interpretation of the results from the micropulse literature is the inconsistency of the laser parameters used. There is a small therapeutic range for subvisible micropulse laser. Laser intensities above this range cause retinal damage and intensities below this range are subtherapeutic. Dorin et al. recommended using pre-specified power adjustments based on a chosen duty cycle in order to achieve consistent therapeutic subthreshold treatment.[76] Desmettre also attempted to define parameters for the use of a micropulse diode laser.[77] He found that no visible burns were seen clinically or on fluorescein angiography when 30% threshold energy was used, but there was evidence of structural damage when higher energy levels were used. He therefore recommended titrating the laser to determine the threshold power (barely visible burn) and then switching to micropulse mode using a 15% duty cycle and increasing the power to 2x threshold to achieve 30% threshold energy. More recently, Luttrull et al. used computational modeling of laser-induced retinal tissue hyperthermia to determine therapeutic thresholds.[78] They recommended using a very low duty cycle (5%) to take advantage of its higher therapeutic window and less chance of incidental retinal injury. They also recommended using a small spot size to minimize heat accumulation and maximize efficiency of heat dissipation. In order to achieve maximum effect, high-density (contiguous) treatment was also recommended.

DISCUSSION

The subthreshold diode micropulse laser may be a very effective, nondamaging, non-invasive treatment for a diversity of medial retinal disease by functioning more like a targeted medicine than a surgical procedure. However, similar to the proper dosing of a medication, it is essential that consistent and data-driven laser parameters be implemented. True therapeutic thresholds based on biochemical responses to the micropulse laser are not well-established and there is significant heterogeneity in the laser parameters used in the micropulse literature. Despite this limitation, there is evidence to suggest that the subthreshold diode micropulse laser is as effective as a conventional focal laser while mitigating iatrogenic collateral retinal damage associated with photocoagulation, such as vision loss due to expanding scotomas, inflammation, fibrosis, hemorrhage, and choroidal neovascularization. The current state of the evidence for the clinical efficacy of micropulse laser is as follows:

- Diabetic macular edema—high-quality evidence;
- Macular edema in RVO—moderate-quality evidence;
- Central serous chrorioretinopathy—low-quality evidence;
- Age-related macular degeneration—low-quality evidence;
- Proliferative diabetic retinopathy—low quality evidence.

With the advent of intraocular steroids and anti-VEGF agents, resolution of exudation can be achieved without damaging the retina. The routine use of conventional focal macular laser as a first-line therapy has significantly declined, as anti-VEGF therapy has become the standard of care in many retina practices. However, there is still a role for focal lasers in the treatment of cases refractory to anti-VEGF, when edema is not involving the central fovea, when follow-up is inconsistent, or when the cost of anti-VEGF therapy is prohibitive for the patient.

The subthreshold micropulse laser may prove to be a completely non-invasive, painless alternative. Moving forward, there needs to be consensus on standardized laser parameters followed by well-designed, large, prospective randomized clinical trials comparing subthreshold laser to treatments currently considered standard of care. However, the available data suggest that the non-damaging laser holds tremendous promise, particularly for diabetic macular edema, and may be a good addition to our current armamentarium for treating medical retinal disease.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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