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Review Article

# SUBTHRESHOLD DIODE MICROPULSE LASER PHOTOCOAGULATION FOR THE TREATMENT OF DIABETIC MACULAR EDEMA: A REVIEW

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## ABSTRACT

Diabetic Retinopathy (DR) is the most common cause of blindness throughout the world. DR leads to Diabetic Macular Edema (DME) when fluid starts to leak from retinal capillaries and causes swelling of the macula. There are many clinical trials demonstrating the benefits of conventional photocoagulation in the treatment of diabetic macular edema and other retinal diseases, but it also have side effects in retina and visual acuity. There is a recent development of Micropulse laser with less side effects than conventional photocoagulation such as scarring of retina, retinal fibrosis, choroidal neovascularization and field sensitivity deterioration and is found to be equally effective as conventional photocoagulation. The aim of this review was to describe principle of Micropulse laser and how it is beneficial in the patient with DME.

**Keywords:** Diabetic Retinopathy, Diabetic Macular Edema, Micropulse laser, Subthreshold photocoagulation, Subthreshold diode Micropulse laser

## INTRODUCTION

Throughout the world Diabetic retinopathy (DR) is the most common cause of blindness[1,2]. There are different stages of DR which are nonproliferative DR (NPDR), proliferative DR (PDR) but the reduction of vision does not depend on the stage of DR. There could be reduction in vision, the vision-threatening DR (VTDR), at any stage of the disease. Likewise, Diabetic macular edema (DME) can also occur in any stage of DR but more commonly seen in NPDR [3]. DME is the most frequent cause of vision loss in the patient with Diabetic mellitus. Estimation was provided by the International Diabetes Federation that 285 million individuals world wide have diabetes mellitus and approximately 14% of this group have DME [4]. The prevalence of diabetes for all age groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people having diabetes is estimated to rise from 171 million in 2000 to 366 million in 2030. The urban population in developing countries is estimated to double between 2000 and 2030 [5]. In the patients with Diabetic mellitus, DR is caused due to the damage to retinal blood vessels. DR leads to DME when fluid starts to leak from retinal capillaries and causes swelling of the macula. Longer duration of diabetes, progression in retinopathy, hyperlipidemia and poor glucose control are the factors leading to DME [6].

The Early Treatment Diabetic Retinopathy Study (ETDRS) defined clinically significant macular edema as (1) thickening of retina at or within 500 um of the center of macula, (2) hard exudates at or within 500um of the center of the macula, if associated with thickening of the adjacent retina or (3) area of retinal thickening greater than or equal to 1 disc area and any part of which lies within 1 disc diameter of the center of the macula [7].

## TREATMENT OPTIONS

There are several types of treatment options for DME including intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents, Intravitreal anti-VEGF agents, either alone or as an adjunct to laser photocoagulation and intravitreal injection of corticosteroids [8]. Surgical option for the treatment of DME is pars plana vitrectomy [9].

### Anti-VEGF injection:

Ranibizumab (Lucentis; Genentech Inc., San Francisco, CA, USA and Novartis Pharma AG, Basel,Switzerland) is a humanized, affinity matured VEGF antibody fragment that binds to and neutralizes all isoforms of VEGF. Aflibercept is fully human, recombinant fusion protein that targets VEGF-A, VEGF-B and placental growth factor. Aflibercept binds all isoforms of VEGF-A with high affinity [10]. Bevacizumab (Avastin®, F. Hoffmann-La Roche Ltd) a full length monoclonal antibody that binds all forms of VEGF-A. It has been used for the treatment of macular edema secondary to DME, as well as in branch retinal vein obstruction

and central retinal vein obstruction and neovascular age related macular diseases [11]. Pegaptanib *(*Macugen, OSI/Eyetech, Melville, NY, USA) is a ribonucleic acid aptamer [12]. It targets the VEGF165 isoform, an especially pro-inflammatory isoform. It inhibits the endothelial mitogen activity of VEGF-A and its vascular permeability effects [13].

## Intravitreal injection of corticosteroids:

Dexamethasone is a potent inhibitor of cytokines released by human pericytes. Intravitreal injection of dexamethasone decreases Intercellular Adhesion Molecule-1 (ICAM-1) mRNA and protein levels, reducing leukostasis and blood retinal barrier (BRB) breakdown. Triamcinolone acetonide (TA) is one of the most commonly used steroid agents for the treatment of retinal conditions. It is synthetic steroid of the glucocorticoid family with a fluorine in the ninth position and commercially available as an ester. Fluocinolone acetonide is a synthetic corticosteroid, with potency similar to the glucocorticoid dexamethasone [14].

## Pars plana vitrectomy:

On performing pars plana vitrectomy (PPV) patients require admission to a hospital is needed which is a disadvantage of PPV. Severe complications like postoperative rhegmatogenous, retinal detachment and neovascular glaucoma can also develop [15].

## Conventional Laser photocoagulations:

There is significant benefit of laser photocoagulation in the treatment of clinically significant DME demonstrated by ETDRS, which showed reduction of incidence of visual loss by approximately 50% [16].

## Disadvantages of conventional laser photocoagulations:

Conventional laser photocoagulations have also found to cause visible scars and also may cause vision decreasing complications like choroidal neovascularization, sub-retinal fibrosis and field sensitivity deterioration [16].Conventional laser treatment also affects macular function [17,18]. Pain discomfort is also experienced by patients during the treatment procedure and the pain characters patients described as sharp, flashing, tiring, intense, piercing, intermittent, and brief [19].

Therefore, different types of laser have been developed over the years based on the lasing mediums, laser delivery system, and wavelengths used. A new approach has been developed called the Subthreshold Micropulse mode which limits the progressive enlargement of the laser scar, causing less injury to the targeted retinal pigment epithelium (RPE) [20]. The Micropulse laser only stimulates the RPE cells inducing biological response that promotes restoration of RPE cells' integrity and physiology (i.e, RPE-pump and blood retinal barrier (BRB) functions) and, ultimately the resorption of the subretinal fluid [21].

## MICROPULSE LASER

### History:

The therapeutic effect of Micropulse laser was first demonstrated in 1997 by Friberg and Karatza. They used Micropulsed 810nm diode laser and concluded that the laser is clinically effective in the treatment of macular edema from diabetic retinopathy and venous occlusion. Their result showed, by 6 months 92% of eye had clinical resolution of macular edema and 77% had stabilization of visual activity in the patient with branch retinal vein occlusion. Clinical resolution of macular edema was seen in 76% of newly treated patients and 67% of previously treated patients with diabetic macular edema by 6 months [22].

### Micropulse operating mode and technology:

In conventional photocoagulation, the continuous wave (CW) laser energy causes a rapid temperature rise that cause 'white' inner retina burn [21]. Where as in MicroPulse laser mode, the CW is delivered as train of repetitive short pulse (typically within 100-300 microseconds) within an 'envelope', whose width is typically within 0.1 - 0.5 second which constitutes the exposure duration. The duration of each micropulse is 'ON' time and the 'OFF' time is the time between two successive micropulses which allows thermal relaxation by allowing the heat to cool down. The period T is the sum of the 'ON' and 'OFF' times and 1/T is its reciprocal which is the repetition rate in pulse per second (pps), also referred as frequency f in hertz (HZ). The duty cycle is the ratio between the 'ON' time and the period 'T', which is in %. Repetition rate and duty cycle determine 'isolation' or 'additivity' of the thermal rise produced by each single micropulse. Isolation of thermal rises requires a relatively long 'OFF' cooling time and this implies a relatively low repetition rate. To minimize the pulse-to-pulse thermal additivity, the repetition rate should not exceed 500 pps. The period T should not be shorter than 2 ms (1/500 s), the "OFF" time should not be shorter than 1.7 msec and the duty cycle should not be higher than 15% [23].

## SUBTHRESHOLD PHOTOCOAGULATION

Subthreshold retinal photocoagulation is the retinal laser that is biomicroscopically invisible at the time of treatment. 'Classical' subthreshold photocoagulation has the thermal burn less visible than the white burn. The 'clinical' subthreshold photocoagulation has lesser laser induced retinal damage, combined with micropulsed laser where the damage is only at the outer retina and RPE. 'Clinical' subthreshold photocoagulation may not be ophthalmoscopically visible at the time of treatment but with time may be visible clinically or in Fundus fluorescein angiography (FFA). 'True' subthreshold photocoagulation produces no damage to retina and are not visible at the time and anytime after the treatment and also can not be distinguished in FFA, Fundus autofluorescence (FAF) and Spectral domain optical coherence tomography (SD-OCT). Thus Subthreshold Diode Mode, is a subtype of Micropulse laser which represents the evolution of

"subthreshold" laser treatment for retinal vascular Disease [24].

## MICROPULSE LASER IN DME

DME patients treated with Subthreshold Diode Micropulse Laser Photocoagulation (SDMLP) have been shown to have less burning/ scarring of retina while it also effectively reduces central foveal thickness. A prospective nonrandomized case series lead by ihab saad Othman and his associates treated 240 eyes from 200 patients diagnosed with nonischemic CSDME (clinically significant diabetic macular edema) with SDMLP. The result showed that, Primary treatment group which included 187 eyes with primary CSDME, there was significant improvement or stabilization of visual acuity after the first 3–4 months was stable thereafter. And in Secondary treatment group which included 33 eyes with recurrent CSDME had stable visual activity[25].

Not only less burning scars in retina and reduced central foveal thickness but also improves visual acuity in the patients with DME. Yoko Takatsuna and associates treated 56 eyes of 44 patients with DME with 810nm SMDLP which was delivered with Iris Medical Oculite SLx. On 1, 3, 6 and 12 months followup examinations, the best-corrected visual acuity (BCVA) and the foveal retinal thickness measured by OCT were done. The mean baseline foveal thickness was 504 um , and it significantly reduced to 439 um at 1 month (P = 0.001), 409 um at 3 months (P <0.0001), 358 um at 6 months (P<0.0001), and 320 um at 12 months (P<0.0001). The mean baseline BCVA was 0.47 logarithm of the minimal angle of resolution (log-MAR) units, which didn't change significantly during followups. Among the 56 eyes, 10 (17.8%) had an improvement of BCVA of >0.2 logMAR units, 36 (64.2%) remained the same, and 10 eyes (17.8%) had reduction of >0.2 logMAR units at 12 months treatment. So, they concluded that SMDLP has a beneficial effect on DME [15].

A Prospective, nonrandomized interventional case series in 36 diabetic patients (43 eyes) with clinically significant DME and a central macular thickness (CMT) of <600 um by optical coherence tomography was carried out in Japanese population. They used 810 nm diode laser photocoagulation device (Iris Medical OcuLight SLx) from Iridex Corp (Mountain View, California, USA) in the micropulse operating mode. Three months follow up after the treatment with subthreshold micropulse diode laser photocoagulation, showed significant CMT reduction but there was no significant improvement in BCVA and macular volume. Preoperative CMT, BCVA (log-MAR) and macular volume were 341.8 +/- 119.0 um, 0.12 +/- 0.20, and 8.763 +/- 1.605 $mm^3$ respectively and on 3 months follow up CMT, BCVA and macular volume were 300.7 +/- 124.1 um, 0.12 +/- 0.21, and 8.636 +/- 1.408 $mm^3$. Visual acuity was improved or maintained within 0.2 logMAR for 12 months in 94.7% of the patients. No visible scars were seen. Here the authors concluded that, in patients with moderate DME, subthreshold diode micropulse laser photocoagulation controls ME and maintains visual acuity with minimal retinal damage and the efficacy of this method in Japanese patients[26].

It also haven been shown that this laser has positive long term followup results. A longest followup study was recently conduced by Sobha Sivaprasad and associates. They conducted a non- comparative case-

series which was 3 year long followup in 25 eyes of 19 patients with DME with presence of EDTRS criteria and best corrected visual acuity of at least 1.0 logMAR were recruited. Here, 810 nm infrared diode laser (Iris OcuLight Micropulse diode photocoagulator, Iridex [UK], Cwmbran, Wales, UK) was used. In this study, the authors concluded that, there is a long term beneficial effect of SDMLP on visual acuity and resolution of clinically significant diffuse diabetic macular edema (CSDME) with minimal chorio-retinal damage [27].

No complications and no laser lesion was seen in 18 eyes of 14 patients with CSDME with foveal thickness more than or equal to 223um, who were treated with low-intensity, high-density SDMLP which was documented by series of Optical Coherence Tomography (OCT) taken at 1, 4, and 12 weeks after treatment [28].

More recently, a study was performed to compare the effect of SDMLP and conventional laser photocoagulation in the treatment of DME. Here, sixty eight eyes of 68 patients were randomly divided into two groups. Group 1 receiving SDMLP and Group 2 receiving conventional laser photocoagulation. On 4 months followup CMT decreased significantly in Group 1 than Group 2. Central macular volume also reduced significantly in Group 1 where as it remained similar in Group 2 in 4 months followup. BCVA also improved significantly in Group 1 but remained unchanged in Group 2. Retinal scar was not seen in Group 1 patients but was seen in all the patients of Group 2[29].

## CONCLUSION

The Subthreshold Diode Micropulse Laser Photocoagulation have proven to be effective in the treatment of Diabetic Macular edema to achieve the desired results. No heavy burns is seen as continuous wave of laser is delivered as train of short pulse with low energy. Not only it is invisible but also there are less side effects. Till date, the studies has show that SDMLP is effective in treating Diabetic Macular edema and can be used as a routine treatment in clinics. Subthreshold Diode Mode is a new technology that will improve our understanding of retinal laser effects and the pathophysiology of the retinal diseases. Further research is required to better understand the mechanism of action of subthreshold laser burns and the required titration for Diabetic Macular Edema and other eye blinding conditions.

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