Editorial

Subthreshold Macular Laser Treatment

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The conventional continous wave (CW) laser photocoagulation, applied either as focal or grid pattern, using green argon laser (514 nm) was shown by the Early Treatment Diabetic Retinopathy Study (ETDRS) to reduce the risk of moderate vision loss (3 lines or more on the ETDRS chart) by 50% and has been the standard of care for DME (diabetic macular edema) since the mid-80s[1]. Although the ETDRS demonstrated that focal/grid photocoagulation improves visual outcome in DME, it should be emphasized that the benefit was in reducing the frequency of visual loss and not in improving visual acuity. More than 3 lines (> 15 letters) of improvement in 3 years has been reported to be only 3% by the ETDRS report[2]. Moreover, conventional laser treatment may be associated with significant destruction of retinal tissue, and heat conduction to the nerve fiber layer and photoreceptors may result in the irreparable thermal destruction. This may cause side effects such as loss of macular sensitivity on microperimetry, progressive enlargement of laser scars towards the fovea, choroidal neovascularisation, epi-submacular fibrosis, iatrogenic foveal coagulation, increased macular edema and central visual acuity loss[3-6]. With anti-VEGF therapy while untoward effects of laser were overcome, it has also been shown to stabilize and increase vision in a significant proportion of patients[7,8]. Nevertheless macular laser is still a choice of therapy because of the following reasons:

1. Anti-VEGF therapy is not without problems. Because of the temporary effectiveness of the injected anti-VEGF drug, repeated intravitreal injections are required which pose the risk of endophthalmitis[9]. Moreover, these repeated injections are a burden for both the patient and the physician.
2. Anti-VEGF therapy is more expensive.
3. Major studies of diabetic macular edema treatment with Intravitreal Anti-VEGF agents have reported that rescue laser treatment was needed in 20 – 56% of patients[10,11].
4. In patients with clinically significant macular edema (CSME) without central involvement, focal laser therapy is still the first line of treatment.
5. There are patients that decline intravitreal injections.
6. There may be systemic factors which anti-VEGF agents may pose risks and preclude anti-VEGF therapy.

Recent understanding of the mechanism of the therapeutic effect of laser photocoagulation has changed. Previously thermal damage to the retinal pigment epithelium (RPE) and photreceptors was desired to decrease the metabolic load and hypoxia and therefore decrease secretion of angiogenic factors from ischemic retina. It is now believed that the therapeutic effect of laser is mediated by the healing response of the RPE to thermal injury and the useful therapeutic cellular cascade is activated, not by laser-killed RPE cells, but by the still-viable RPE cells surrounding the burned areas that are affected by the heat diffusion at sublethal thermal elevation[12,13].

What are the cascade of events triggered by macular laser photocoagulation and leading to the resolution of edema?

It was thought that absorption of laser energy within the retinal capillaries had a direct occlusive effect on leaky microaneurysms, however the exact role of grid laser has not been understood. More recently, it has been recognized that the therapeutic effect of laser results from sublethal irradiation of the RPE followed by the release and/or downregulation of various factors from recovering RPE cells. These factors are cytokines, VEGF, heat shock protein, pigment epithelium-derived factor (PEDF), and matrix metalloproteinases (MMPs). Laboratory studies have shown that subsequent to laser irradiation, within 7 days RPE cell migration and enzyme release occurs which facilitates removal of debris from Bruch's membrane and increases transport processes. RPE cell division occurs by 7 – 14 days and is associated with release of cytokines, which trigger vascular endothelial cell division which strengthen the neuroretinal capillaries, leading to increased water outflow from the retina and reduced water inflow into the retina inducing reduction of retinal edema[14,15]. New understanding of the therapeutic effects of laser treatment have brought the concept of new modalities of laser treatment without damaging the retina. All new modalities intend to create subthreshold treatment. Subthreshold photocoagulation is defined as laser treatment which produces absolutely no retinal damage detectable by any method including FFA (fundus fluorescein angiography) and newer high-resolution retinal imaging methods such as FAF (fundus autofluorescence) and SD-OCT (spectral domain-optical coherent tomography) at the time of treatment or anytime thereafter[16].

Subthreshold Laser Modalities (Table 1.):

- Subthreshold diode micropulse laser (SDMPL). (Manufacturing Companies:Iridex, Quantel).
- Yellow wavelength subthreshold micropulse laser (Manufacturing Companies:Iridex, Quantel, OD-OS).

SDMPL (subthreshold diode micropulse laser) is the laser technique that has been on the market the longest and has been used the most. Recently yellow wavelength micropulse mode has also become available. In 1990, Pankratov reported development of a new laser modality designed to deliver laser energy in short pulses ("micropulses") rather than as a continuous wave[17]. Micropulse laser uses a laser beam that is chopped into short, repetitive microsecond pulses, aiming tissue to cool between pulses and reducing thermal buildup. The laser "on" time is the duration of each micropulse, the "off" time is the time between micropulses that allows for heat reduction and thermal isolation of each pulse. The ratio between "on" and "off" time is the duty cycle. The lower the duty cycle is, the greater the heat reduction is. Duty cycle can be adjusted and is commonly set at 5%. Pulse duration of 200ms with 5% duty cycle means: An envelope of 100 x (100 µsn on +1900 µsn off) laser pulses. There are small scale randomised controlled clinical trials as evidence comparing subthreshold micropulse to conventional macular laser. Most studies have found better visual results and equal efficacy for macular edema[18-22]. There is also a meta-analysis of those randomised controlled clinical trials which has found slightly better visual outcomes with subthreshold micropulse laser and similar effect on central macular thickness[23]. MPL is applied in a grid pattern with no spacing between spots, spot size is usually 160 – 200 µ, distance from foveal center is 500 microns. Usually using 5% duty cycle, the energy needed for a barely visible treatment effect, which is the threshold energy is determined and half of the energy needed for a threshold burn is used for treatment. Treatment parameters like duty cycle, spot size and the method of determination of the threshold energy whether by using continuous wave laser and then switching to micropulse mode or by using micropulse mode to determine threshold energy may differ among published studies.

Table 1: Subthreshold Lasers.

Laser Type	Mode	Wavelength
Subthreshold micropulse*	Pulsed	Diode(810nm), yellow (577 nm)
Non damaging retinal laser therapy (NRT)	Continuous	Yellow (577nm)
Retina rejuvenation therapy (2RT)	Pulsed	Frequency doubled Nd: YAG laser 532 nm
Selective Retinal Therapy (SRT)#	Pulsed	Frequency doubled Nd: YLF laser 527 nm

Legend for Table 1:

*: Also named as MicroPulse, SubLiminal, Micro Second according to manufacturing company.

#: Although reported as subthreshold, treatment effect can be determined by FFA.

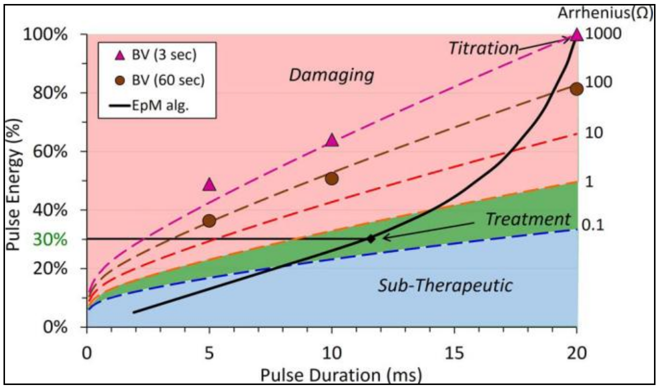

Fig. 1:

Legend for Fig. 1:

Dashed lines, corresponding to different clinical grades, differ by an order of magnitude in Arrhenius integral X. The red area corresponds to the damaging settings and green to the nondamaging range of HSP expression; blue is below the threshold for cell response. Titration of 100% corresponds to barely visible lesion (BV) observed at 3 seconds.

Lavinsky D, Wang J, Huie P, et al. Nondamaging retinal laser therapy:rationale and applications to the macula. Invest Ophthalmol Vis Sci.2016;57:2488–2500.

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Fig. 2:

Legend for Figure 2:

Fundus autofluorescence image of a patient treated with NRT. White arrows demonstrate hyperfluorescent test spots. No treatment effect is seen at the macula.

Non-damaging retinal laser therapy (NRT) (previously named EpM) (Manufacturing Company: Topcon)

Heating of biomolecules by laser energy leads to protein denaturation as a temperature dependent chemical reaction. Above a certain threshold cellular necrosis and coagulation occurs. The technique NRT is based on the Arrhenius equation which is a computational tissue temperature model that was obtained by animal experiments. By the Arrhenius equation it has been shown that at a certain pulse duration, 30% of the barely visible treatment effect which is termed as the threshold energy has been shown to be the highest non damaging and also the level that has therapeutic effect illustrated by the green shaded area (Fig. 1). Above 30% of the threshold energy has been shown to be damaging and below 30% of the threshold energy has been shown to be sub-therapeutic[24]. By animal experiments of retinal laser therapy and immuno-histochemical staining for heat shock proteins (HSP), it has been shown that with 100% threshold energy, no HSP expression is seen over the laser treated area demonstrating cell death over the laser treated area with HSP expression sorrounding the laser burn, implying there has been sublethal thermal elevation sorrunding the laser burns. With 30% threshold energy, as HSP is expressed over the laser spots, it is shown that cells are not damaged over the laser treated areas. Laser induction of HSP by thermal stress, is thought to rejuvenate RPE cells and restore their function[25,26]. Promising results have been reported for chronic central serous chorioretinopathy and MacTel type 2 but there has been limited experience[24]. NRT is applied in a grid pattern with 0.25 spot spacing between spots, spot size is 200µ, duration is 15ms. Distance from foveal center is 500 – 700 microns. The energy needed for a barely visible treatment effect, which is the threshold energy is determined and 30% of the energy needed for a threshold burn is used for treatment.

Retina rejuvenation therapy (2RT) (Manufacturing Company:Ellex)

With 2RT, laser mode is discontinuous and the pulse duration is even shorter, it has been reduced to 3ns. Subthreshold laser power is used. This results in damage from cavitation rather than thermal interaction, only few RPE cells are damaged without causing Bruch's membrane rupture. Each of the dead RPE cell is surrounded by unaffected RPE cells. The overlying photoreceptors do not undergo secondary cell death. A pilot clinical study about the technique has been published, reporting visual acuity improvement and reduction in macular thickness[27].

Selective Retinal Therapy (SRT)

(Manufacturing Companies:Medical Laser Center, Lumenis)

SRT has been developed to further improve selectivity by using a much shorter pulse duration of 1.7 µs, and consequently a higher irradiance. It has been demonstrated in animal studies that selective treatment of the RPE is achieved using microsecond pulse durations, and the follow-up showed that the RPE regenerates with survival of the adjacent photoreceptors[28]. There are few clinical studies evaluating SRT in diabetic macular edema. Stabilisation of visual acuity or improvement in over 80% of patients have been reported. This treatment although described as subthreshold, has FFA findings indicating RPE damage[29].

Limitations of Subthreshold Lasers

The primary limitation is the absence of a visible end point during treatment and determination of threshold energy out of the macular area which leads to concerns of under treatment. For micropulse lasers the lack of standardized treatment parameters are other major limitations as laser settings can be different depending on the study, with various duty cycles, spot sizes, and durations. Large scale randomised controlled trials are required for comparison with conventional laser, anti-VEGF treatment and combined anti-VEGF with subthreshold laser therapy to find out the actual role of these several techniques of subthreshold laser treatment in various causes of macular edema and macular pathologies.

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