Comparison of different settings for yellow subthreshold laser treatment in diabetic macular edema

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Abstract

Background: To assess the safety and efficacy of two subthreshold parameters (5 and 15% duty cycle (DC)) compared to standard ETDRS (early treatment of diabetic retinopathy study) continuous wave (CW) laser.

Methods: In this prospective randomized study, 30 eyes from 20 patients with non-center involving macular edema were randomized into 3 different groups: 5% DC, 15% DC and CW navigated modified ETDRS laser treatment. Titration in subthreshold groups was performed with 30% of the threshold power, decided with microsecond pulses. CW laser was titrated to a barely visible burn. All patients underwent microperimetry, thickness measurements and visual acuity examinations at baseline, 6 weeks and 12 weeks post treatment.

Results: At three months follow up, retinal sensitivity was significantly reduced in the CW group by −2.2 dB whereas in both subthreshold groups, retinal sensitivity increased by 2.4 dB for 5% and 1.9 dB for 15% DC with no significant difference. Retinal volume (mm3) decreased in both subthreshold groups by 0.08 ± 0.3 and 0.12 ± 0.11 in 5 and 15% DC group respectively. Whereas the CW group showed volume increase of 0.55 ± 0.92 (p = 0.02 and 0.01 for 5 and 15% DC groups). Visual acuity remained stable in all 3 groups (−0.7 letter in 5% DC; 2.11 letters in 15% DC and 0.88 in CW with no significant difference).

Conclusion: Subthreshold microsecond laser was shown to be safe and effective with both 5 and 15% DC as compared to conventional photocoagulation with ETDRS parameters. The 15% DC setting trended to achieve better anatomical, visual and functional outcomes.

Trial registration: Retrospectively registered (NCT03571659, 06/26/2018).

Keywords: Subthreshold laser, Microsecond, Micropulse, Diabetic macular edema, Microperimetry, Laser photocoagulation

Background

After various randomized and non-randomized clinical trials, anti-vascular endothelial growth factor (VEGF) therapy has become a gold standard in management of diabetic macular edema [1–5]. However, in the RISE and RIDE trials, the Phase 3 trials for ranibizumab in diabetic macular edema, 13.9% of patients receiving monthly intravitreal injections of ranibizumab showed no gain of letters compared to baseline at 24 months [3]. Frequent visits with frequent injections, causes a major economic burden for these patients. In a study from Wallick et al., patients with diabetic macular edema were found to have, on average, 25.5 annual days with a health care related visit [6]. In a Canadian study published in 2014 by Gonder et al., the mean 6-month DME-related cost was $2092 per patient [7]. The present day cost is likely higher since the study considered that 70% of patients were injected with bevavizumab and the rest with ranibizumab. Thus, there is a constant need for a therapy with long term efficacy for this visually debilitating disease.

Laser photoagulation was proposed as treatment of choice for diabetic macular edema after ETDRS (Early Treatment of Diabetic Retinopathy Study) [8], much before the anti-VEGF era. Maintenance rather than the
vision improvement along with the loss of contrast sensitivity, poor color vision, accidental foveal damage and expansion of macular scars were the primary complication of laser photocoagulation, which brought the laser photocoagulation in the back seat. However, in recent past with improved technology, subthreshold laser photocoagulation has got more interest and shown to be effective in various macular diseases such as diabetic macular edema [9–13], CSCR (central serous chorioretinopathy) [14–16], and venous occlusions [17].

Laser parameters were standardized after ETDRS study for diabetic macular edema [15]. Unlike conventional laser photocoagulation, there is no standard parameters have been proposed for subthreshold laser. In the literature, there is a lot of variability for subthreshold laser settings in terms of titration, duty cycle (ranging from 5 to 15% duty cycle (DC)), laser power and pulse duration.

This study aims to assess the safety and efficacy of two of the most frequently used subthreshold parameters (5 and 15% DC) when compared to standard ETDRS threshold laser.

Methods
This prospective randomized double-masked pilot study was performed at L V Prasad eye institute, Hyderabad. The study was approved by the institutional review committee and adhered to the tenets of the Declaration of Helsinki. All participants gave written informed consent before enrollment in the study. The Hyderabad Eye Research Foundation, India, supported this study. Patients were recruited from January 2012 through February 2013 at LV Prasad Eye Institute, Hyderabad, India.

Patient eligibility
Inclusion criteria: Eyes with naive non-center involving macular edema (central subfield thickness less than 350 μm) with visual acuity 20/30 or better. The key exclusion criteria were: (1) Dense lens opacity impeding the visualization or laser photocoagulation; (2) Previous macular laser photocoagulation in the study eye; (3) Use of intraocular or periocular corticosteroids in the study eye within the previous 3 months; (4) Previous treatment with anti-VEGF drugs in the study eye.

Study design
Subjects were randomized into 3 different groups. Groups A and B received navigated microsecond laser treatments at 5% DC (100 μs on time) and 15% DC (300 μs on time), respectively. Group C received a continuous wave (CW) navigated ETDRS threshold laser treatment with visible endpoints. In situation when both eyes of the patient were eligible, each eye was randomized as per the randomization. Patient and the visual acuity assessor were masked.

Color fundus photograph
Color fundus photographs of the optic disc, macula, and temporal retina (30°) were captured with a mydriatic camera (Zeiss FF450, Carl Zeiss Meditec, Jena, Germany).

Fundus fluorescein angiography (FFA)
FFA was performed using fluorescein sodium 20% and imaging on Navilas® system (OD-OS GmbH, Teltow, Germany) to determine the site of leakage at baseline, and at three months from baseline.

Spectral Domain Optical Coherence Tomography (SD-OCT):
Cirrus HD-OCT (Carl Zeiss Meditec, Inc., Dublin, CA.) was used to obtain SD-OCT scans. Scanning protocol included HD5 line raster, HD single line raster, enhanced depth imaging, and macular cube. Central retinal thickness (CRT) (1 mm central retinal thickness area as described in the Early Treatment Diabetics Retinopathy Study (ETDRS) fields) was determined automatically and analyzed by OCT software, by generating images using the Macular Cube 512 × 128 scan over 6 × 6 mm area, the cube being composed of 128 horizontal examination lines of 512 A-scans each.

Microperimetry (MAIA™, Centervue, Padova, Italy)
Microperimetry was performed using the microperimeter (MAIA™, Centervue, Padova, Italy) after dilation of pupils. Goldmann III stimuli and a 4–2–1 staircase strategy with a test grid with 37 stimulus locations covering an area of 10 degrees was applied. Fixation was tracked using built-in fixation target. The stimuli were projected on a white background with black illumination set to 1.27 cd/m2 and a stimulus presentation time of 200 milliseconds. Mean differential light sensitivity in decibels (dB) of all test locations was analyzed for the study. Three fixation classes were defined: stable, relatively unstable, unstable. Stable if more than 75% of the fixation points were inside the 2 degree diameter circle; relatively unstable if less than 75% were inside the 2 degree diameter circle, but more than 75% inside the 4 degree diameter circle; and unstable if less than 75% of the fixation sites were inside the 4 degree diameter circle. A change in sensitivity of 1 dB or more, a change in stability of fixation, or both was considered significant.

All patients underwent microperimetry, thickness measurements and visual acuity examinations at baseline, 6 weeks and 12 weeks post treatment.

Laser photocoagulation
Subthreshold laser used was 577 nm navigated laser using Navilas® system (OD-OS GmbH, Teltow, Germany), however, conventional laser was 532 nm using PASCAL® (OptiMedica) system. Both subthreshold laser groups (A and B) were treated with confluent grids to cover areas of
diffuse edema whereas the threshold laser group was treated with mETDRS modified grids. Fluorescein angiography was used to identify and target leaking microaneurysms, which were targeted directly using navigated laser in all groups.

Titration and settings: Titration in subthreshold groups (5 and 15% DC group) was performed with microsecond pulses to a barely visible burn, after which power was reduced to 30% to reliably achieve subthreshold effects. CW laser was titrated to a barely visible burn. Spot size and envelop pulse durations was set to 100 μm and 100 ms for each group.

**Table 1** Baseline Characteristics of study groups

|                  | Group A (5% DC) | Group B (15% DC) | Group C (CW) |
|------------------|-----------------|------------------|--------------|
| Number of eyes   | 10              | 10               | 10           |
| Mean duration of diabetes (years) | 6.5 ± 1.3      | 7.1 ± 1.1        | 6.3 ± 2.1    |
| Mean age (years) | 58 ± 6.6        | 59 ± 6           | 57 ± 10.6    |
| Lens status      | Clear (5), NS1(2), NS2 (3) | Clear (5), NS1(4), NS2 (1) | Clear (4), NS1(4), NS2 (2) |
| Mean BCVA (ETDRS letters) | 76 ± 10        | 80 ± 5           | 80 ± 7       |
| Mean CMT (microns) | 258 ± 28    | 255 ± 58         | 248 ± 37     |
| Retinal Sensitivity (dB) | 19 ± 5       | 22 ± 4           | 23 ± 4       |

**BCVA** Best corrected visual acuity  
**CMT** Central Macular Thickness

Results

Thirty eyes of 20 patients with a mean age of 57 ± 8.7 years were enrolled in the study with 10 eyes in each group. Sixteen were males and four were females. At presentation, lens status was clear in 14 eyes; grade 1 nuclear sclerosis 10 and grade 2 nuclear sclerosis in 6 eyes. Baseline clinical characteristics of the groups are shown in Table 1. There was no significant difference between the groups for BCVA, CMT and retinal sensitivity.

The laser parameter used for each group is listed in Table 2. The number of spots applied was significantly lower in group C (CW) as CW laser for modified grid was one burn width apart unlike subthreshold group where confluent laser applications were performed. Representative cases are shown as Figs. 1, 2, and 3. As expected the adjusted laser power values were significantly higher in the 5%DC group as compared to 15%DC and CW. This can be attributed to the titration paradigm as the power has to be increased in order to obtain a barely visible burn to compensate the fact of a chopped microsecond pulsing laser beam. Nevertheless, the fluence in both subthreshold groups is comparable and represents about 30% of the threshold energy obtained with CW lasers.

No complications were reported in any of the groups except in one eye of the 15% DC group, the evidence of the microsecond laser was detected at three months with Kruskal-Wallis-Test. P-value of < 0.05 was considered as statistically significant.

**Table 2** Laser parameter characteristics among different groups

|                        | Group A (5% DC) | Group B (15% DC) | Group C (CW) |
|------------------------|-----------------|------------------|--------------|
| Number of spots applied | 435 ± 282       | 335 ± 313        | 128 ± 112    |
| Fluence applied mJ/mm² | 144.4 ± 28.8    | 167.8 ± 28.7     | 488.2 ± 142.4 |
| Power range used in mW (range) | 424 ± 92.8 (220–500) | 168 ± 42.9 (130–280) | 87.3 ± 37.2 (50–180) |
follow up on fluorescein angiography. This patient was therefore excluded from further evaluation.

**Outcome measures**
Changes in primary and secondary outcome measures are shown as Table 3.

**Retinal sensitivity outcome**
At three months, the retinal sensitivity was slightly reduced in the CW group by −0.3 dB whereas in both subthreshold groups, retinal sensitivity increased by 0.9 dB for 5% and 1.7 dB for 15% DC ($p = 0.6$ and 0.2 as compared to threshold group) from baseline.

**Visual acuity outcome**
Best corrected visual acuity remained stable during the follow up period in all 3 groups with no significant difference among the groups (0.7 letter losses in 5% DC; 1.9 letters gain in 15% DC and 0.5 letters gain in CW, respectively). As indicated in Fig. 4 the 15% DC group demonstrated an improvement ($p = 0.04$). Change in BCVA is shown as Fig. 4.
Anatomical outcome

Retinal volume and central retinal thickness remained stable at three months follow up, with a slight trend toward decreasing in both subthreshold groups with 0.08 ± 0.3 in 5% DC group and 0.12 ± 0.11 in 15% DC group. Whereas, CW group represented a slight volume increase of 0.55 ± 0.92 ($p = 0.02$ and 0.01 for 5 and 15% DC groups as compared to threshold group). The same applies to the CRT where a positive development of reduced CRT can be noted as compared to an increase in CRT in the CW group (See Fig. 5).

Discussion

Subthreshold microsecond laser is a novel, tissue-sparing approach to treat diabetic macular edema. Unlike with conventional focal laser, there is no standard protocol for laser settings for subthreshold treatments. Tables 4 and 5 shows an overview of studies on subthreshold laser (including 810 nm and 577 nm) and the myriad of parameters used in diabetic macular edema [9–12, 18–26]. Vujosevic et al. compared yellow with infrared subthreshold laser in 26 and 27 eyes respectively, and found no differences in central retinal thickness, macular volume, foveal choroidal thickness, and best-corrected visual acuity [23]. Our study shows that the subthreshold microsecond laser was safe and effective with both 5 and 15% DC following careful titration as compared to CW laser. In trend, 15% DC setting seems to achieve highest ETDRS letter gain and largest decrease in volume.

Lavinsky et al. did a detailed analysis of retinal structures changes under certain fluence reductions and concluded that 30% of threshold energy does not create any tissue defects [27, 28]. Our parameters cannot be compared directly as Lavinsky et al. used CW mode with 7-10 ms pulse durations. However, considering that shortening the pulse duration results in lesser damage, we performed subthreshold microsecond laser with 30% of threshold laser power and found it to be successful. Therefore, these settings can be considered as safe and effective with microsecond laser.

**Table 3 Change in outcome measures at week 12**

| Parameters                  | CW        | 5%        | 15%       |
|-----------------------------|-----------|-----------|-----------|
| Retinal sensitivity (dB)    | 2.2 ± 2.4 | + 2.4 ± 6.0 ($p = 0.3$) | + 1.9 ± 4.1 ($p = 0.2$) |
| ETDRS letters loss/gain     | 0.9 ± 2.5 | −0.7 ± 7.7 ($p = 0.6$) | 2.11 ± 2.5 ($p = 0.2$) |
| Central Retinal Thickness (microns) | 12.3 ± 41.2 | −12.4 ± 36.6 ($p = 0.2$) | 0.6 ± 21.3 ($p = 0.5$) |
| Retinal volume (mm³)        | 0.55 ± 0.92 | −0.08 ± 0.3 ($p = 0.02$) | −0.12 ± 0.11 ($p = 0.01$) |

*ETDRS Early Treatment Of Diabetic Retinopathy Study

* Compared to CW (conventional) threshold laser
One of the challenges with micropulse is the invisibility of laser applications, which makes it difficult to follow up the patients and re-treatment. NAVILAS® provides an additional advantage over other micropulse laser systems is that it provides the reports with treated area along with laser parameters. Application of confluent laser marks could be challenging using conventional slit lamp laser systems due to eye movement and the unavailability of eye tracking. NAVILAS® provides a computerized laser planning and eye tracking during laser application which is accurate and beneficial for subthreshold laser as the laser spots are not visible. Two studies have shown that use of the NAVILAS® results in higher accuracy of targets for photocoagulation compared to the conventional method without the navigating system [29–31]. However, previous reports suggest subthreshold laser application in the “whole posterior pole” which doesn’t require the information about the previously performed subthreshold laser applications. [32, 33]

Luttrull et al. showed increased burn risk for 810 nm subthreshold laser with more than 5%DC. [34] This risk increases with decreasing wavelength, which may have been the reason for visible burn in one out 10 eyes with 15%DC. This needs further clarification in terms of safety with larger sample size including 5%DC group. However, this study supports the safety of subthreshold laser over the CW laser.

Limitations of our study include small sample size in each group and short follow up. Our study did not scientifically analyze microaneurysm closure rate. However, this is the first study, which compares effect of different duty cycle subthreshold dosage with standard ETDRS laser dosage in diabetic macular edema. However, less number of subthreshold laser applications over a limited area of DME may be the reason for suboptimal response. Due to ethical issues, we did not include center-involving edema, which may have responded differently due to more severity and further loss of retinal sensitivity, and may have influenced the outcome measures.
### Table 4 Overview on parameters used in 810 nm subthreshold laser treatments

| Author                | Wavelength (nm) | Spot size (um) | Duration (ms) | Duty Cycle | Power definition method |
|-----------------------|-----------------|----------------|---------------|------------|-------------------------|
| Laursen et al. [9]    | 810             | 125            | 100           | 5%         | 50% of barely visible burn |
| Figueira et al. [10]  | 810             | 125            | 300           | 30%        | 200% of barely visible burn |
| Lavinsky et al. [11]  | 810             | 125            | 300           | 15%        | 120% of barely visible burn |
| Vujosevic et al. [12] | 810             | 125            | 200           | 5%         | 750 mW                  |
| Luttrull et al. [19]  | 810             | 125            | 300           | 5%         | 750 mW                  |
| Sivaprasad et al. [20]| 810             | 125            | 200           | 5%         | 100% of barely visible burn (unless more than 1200 mW in which case duty cycle was increased to 10%) |
| Othman et al. [21]    | 810             | 75–125         | 300           | 15%        | 100% barely visible burn |
| Inagaki et al. [22]   | 810             | 200            | 200           | 15%        | 200% barely visible burn |

### Table 5 Overview on parameters used in yellow (577 nm) subthreshold treatments

| Author                | Spot size (um) | Power (µW) | Duration (ms) | Fluence (mmJ/mm²) | Power definition method |
|-----------------------|----------------|------------|---------------|-------------------|-------------------------|
| Kwon et al. [24]      | 100            | 20         | 15%           | 140               | Titratin in cw; starting at 100 mW upwards until barely visible burn; after switch to µp power remains immediately below test burn |
| Vujosevic et al. [23] | 100            | 200        | 5%            | 250               | Fixed power setting |
| Yadav et al. [25]     | 100            | 200        | 10%           | 70–200            | Titratin burn in cw, until mild retinal whitening; then µs mode and Half power |
| Inagaki et al. [22]   | 200            | 200        | 15%           | 204               | Test burn in cw mode with 100 ms and 200 µm; then switch to 15% DC and doubling the power which is 60% of threshold energy |
| Pei-pei et al. [30]   | 60             | 10         | 100%          | 324 J/cm²        | 50% of power, no switch of Pulse duration |

### Conclusion

In conclusion, our pilot study reports the subthreshold laser with 15% DC appears to be more efficacious to reduce the retinal thickness and improve the retinal sensitivity, however, safety needs further evaluation on larger studies. Further studies are warranted to evaluate subthreshold laser in center-involving diabetic macular edema with or without anti-VEGF therapy. Subthreshold laser could be considered as cheap treatment option and finally a retinal restorative therapy without any structural and functional damage.

### Abbreviations

BCVA: Best Corrected Visual Acuity; CMT: Central Macular Thickness; CRT: Central Retinal Thickness; CSCR: Central Serous Chorioretinopathy; CW: Continuous Wave; DC: Duty Cycle; DME: Diabetic Macular Edema; ETDRS: Early Treatment Diabetic Retinopathy Study; FFA: Fundus Fluorescence Angiography; SD-OCT: Spectral Domain Ocular Coherence Tomography; VEGF: Vascular Endothelial Growth Factor

### Availability of data and materials

All data were available upon request. In case of any further information, Dr. Jay Chhablani can be contacted at jay.chhablani@gmail.com.

### Author’s contributions

Conception and design: JC, RN, AM; Data collection: JC, RN, AG, AM. Analysis and interpretation: JC, RA, DTK; writing the article: JC, RA, DTK. Critical Revision of the article: JC, RA, DTK, RN, AG, AM. Final approval of the article: JC, RA, DTK, RN, AG, AM.

### Ethics approval and consent to participate

Approval from 1Institutional Review Board, L V Prasad Eye Institute, Hyderabad, India. The study was conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from patients.

### Consent for publication

Not applicable.

### Competing interests

Jay Chhablani is a member of the editorial board.

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