



Original research

Effects of subthreshold diode micropulse laser photocoagulation on treating patients with refractory diabetic macular edema

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Abstract

Purpose: To evaluate the effects of subthreshold diode micropulse laser photocoagulation on treating patients with refractory diabetic macular edema (DME).

Methods: This randomized clinical trial recruited patients with DME in both eyes that were resistant to treatment with intravitreal bevacizumab (IVB). The eyes were randomly divided into two groups who received laser therapy and IVB, or IVB alone. Subthreshold diode micropulse laser photocoagulation and IVB injection were administered in one eye, and an IVB injection was administered in the second eye. IVB injections were repeated in both eyes within one month and two months after the first injection. Best corrected visual acuity (BCVA) logarithm of the minimum angle of resolution (logMAR) and central macular thickness (CMT) were measured before, within a month, and three months after start of intervention.

Results: In this study, 42 eyes of 21 patients were evaluated. The mean age of patients was 60.86 ± 8.57 years. Ten patients (47.6%) were male. Within-group analysis showed a significant decreased in BCVA logMAR in the laser + IVB group reflecting improvement in visual acuity (VA) ($P < 0.001$); it increased in the control group during study reflecting more vision loss ($P = 0.01$). In the laser + IVB group, a significant decrease in mean \pm standard deviation (SD) CMT at 3 months compared to baseline was observed (baseline: 513 ± 126.29 vs. three months: 408.1 ± 95.28 ; $P < 0.001$). The mean \pm SD CMT was significantly lower in the laser + IVB group of eyes than in the control group three months after intervention ($P = 0.02$).

Conclusion: Using subthreshold diode micropulse laser photocoagulation in combination with IVB can significantly reduce CMT and improve BCVA in patients with refractory DME.

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Keywords: Lasers; Macular edema; Diabetic retinopathy; Photocoagulation

Introduction

Diabetic macular edema (DME) is one of the main causes of visual impairment in adults over 50 years of age.¹ Visual impairment has adverse effects on the quality of life of patients and needs proper treatment. The prevalence of DME is 0–3% in newly diagnosed diabetic patients and 28–29% in patients who have had diabetes for more than 30 years.²

The pathophysiology of DME is multifactorial, including an increase in the vascular endothelial growth factor (VEGF)

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and other vitreous inflammatory factors. Long lasting hyperglycemia can cause changes in the microvascular cellular structure of the retina and damage pericytes that modulate capillary perfusion.³ Microvascular impairments cause capillary non-perfusion and retinal ischemia that lead to VEGF release and inflammatory markers that play an essential role in angiogenesis and vascular permeability.⁴

There are several treatments for DME, including intravitreal injection of steroids or anti-VEGF, focal and grid laser photocoagulation, and vitrectomy.⁵ DME is sometimes resistant to multiple therapies and may need more treatment modalities. Studies evaluated the effects of laser photocoagulation on improving DME, and visual acuity (VA) demonstrated that this type of therapy could reduce the risk of visual impairment by 50%.⁶ Conventional laser photocoagulation has several complications based on previous studies, including visible expanding scars, visual field loss, subretinal fibrosis, and choroidal neovascularization.^{7,8} Reducing laser exposure duration and using a subvisible clinical endpoint for therapy can decrease these complications.^{9,10} Subthreshold diode micropulse laser photocoagulation has these two properties. Few studies have evaluated the effects of this type of laser photocoagulation on improving VA and DME with less laser-induced chorioretinal damage.¹¹ In some studies, a combination of laser treatment and medication, such as dexamethasone, was effective and safe for the treatment of resistant DME.¹²

Prompted by the limited number of studies evaluating the effects of subthreshold diode micropulse laser photocoagulation and the necessity to treat patients with DME with fewer complications, this study was designed to assess the impact of this type of laser photocoagulation on treating patients with refractory DME.

Methods

This randomized clinical trial recruited patients presenting to the hospital from 2016 to 2017 with DME in both eyes resistant to treatment with intravitreal bevacizumab (IVB). The inclusion criteria included 1) patients with DME in both eyes resistant to treatment with IVB, 2) no history of medication other than IVB or any type of laser photocoagulation, 3) no history of significant cataracts and cataract surgery over the previous three months, 4) no history of vitrectomy surgery or other intraocular surgeries on the eyes, and 5) patient willingness to participate in the study. Patients who had macular edema due to causes other than diabetes, those who had experienced retinal detachment or intravitreal hemorrhage due to intravitreal injections, and those who discontinued participation in the study were excluded. If three injections of IVB did not reduce central macular thickness (CMT) to less than 300 μm, or the thickness of the CMT did not decrease by more than half the increased amount of 300 μm, the macular edema was considered resistant to treatment.¹³

Participants were interviewed to collect demographic information, including age and gender. They underwent ophthalmological examinations with the slit-lamp and indirect

ophthalmoscopy with a 90° D lens. The Early Treatment Diabetic Retinopathy Study (ETDRS) visual chart was used to measure VA at 4 m. Optical coherence tomography (OCT) was done by SD-OCT Heidelberg engineering (Heidelberg, Germany) to evaluate CMT. Then one eye of patients was selected to receive laser therapy and IVB based on the random allocation system, and the other eye was selected to receive IVB. The injection was performed for each eye separately with a one-week interval. Subthreshold diode micropulse laser photocoagulation (810 nm, with 200 nm spot size, 5% duty cycle, and with power four times more than at least visible effect, Iridex IQ 532 micro-pulse device manufactured by Iridex-USA) in the macular area (the multifocal grid pattern laser was performed in the region of the edema), and IVB injection were administered for the first eye based on standard protocols. IVB injection was administered for the second eye of patients as a control. After one month, patients were examined again to assess best corrected visual acuity (BCVA) and CMT. Then IVB injection was repeated at one month and two months after the first injection for both eyes of patients. At the end of the study (one month after the 3rd injection), BCVA and CMT were assessed in both eyes of patients. The same expert ophthalmologist carried out the laser therapy and IVB injections.

Data was analyzed in SPSS version 22 (SPSS Inc., Chicago, IL, USA). BCVA was transformed into logarithm of the minimum angle of resolution (logMAR) for statistical analysis. Quantitative and qualitative data were presented by mean ± standard deviation (SD) and number or percentage, respectively. Data was compared between both eye groups with the independent *t*-test. Changing variables at different times were compared by repeated measures ANOVA. A *P* value 0.05 was considered significant.

Results

In this study, 42 eyes of 21 patients were evaluated. The mean age of patients was 60.86 ± 8.57 years, and 10 of them were male (47.6%). The range (minimum–maximum) of VA in IVB group and IVB + laser was 20/500–20/40 and 20/500–20/50, respectively. There were no significant age and gender differences between the groups (*P* > 0.05).

Table 1 demonstrates the trend of BCVA logMAR change in both the groups during the study. The mean ± SD BCVA logMAR was not significantly different between the two

Table 1
The best corrected visual acuity (BCVA) logarithm of the minimum angle of resolution (logMAR) of patients at different evaluation times.

Variables	Before	One month	Three months	<i>P</i> value ^a
BCVA Laser + IVB	0.81 ± 0.33	0.74 ± 0.28	0.62 ± 0.26	<0.001
logMAR IVB	0.70 ± 0.33	0.75 ± 0.33	0.79 ± 0.33	0.01
<i>P</i> value ^b	0.29	0.95	0.08	

BCVA: Best corrected visual acuity; logMAR: Logarithm of the minimum angle of resolution; IVB: Intravitreal bevacizumab.

^a Repeated measure ANOVA.

^b Independent *t*-test.

Table 2
The central macular thickness (CMT) of patients at different evaluation times.

Variables	Before	One month	Three months	<i>P</i> value ^a
CMT Laser + IVB	513 ± 126.29	454.62 ± 94.79	408.1 ± 95.28	<0.001
IVB	494.38 ± 130.7	492.14 ± 130.27	502.38 ± 145.88	0.64
<i>P</i> -value ^b	0.64	0.30	0.02	

CMT: Central macular thickness, IVB: Intravitreal bevacizumab.

^a Repeated measure ANOVA.

^b Independent *t*-test.

groups of eyes before ($P = 0.29$), one month ($P = 0.95$), and three months after intervention ($P = 0.08$).

Within-group analysis showed a significant decrease in BCVA logMAR in the laser + IVB group, reflecting improvement in VA ($P < 0.001$); it increased in the control group during study reflecting more vision loss ($P = 0.01$) (Table 1).

Table 2 demonstrates the trend of CMT change in both the groups during the study.

The mean ± SD CMT was not significantly different between the two groups of eyes before ($P = 0.64$) and one month after intervention ($P = 0.30$). The mean ± SD CMT was significantly lower in the laser + IVB group of eyes than in the control group three months after intervention ($P = 0.02$) (Table 2).

Within-group analysis showed a significant decrease in mean ± SD CMT at 3 months compared to baseline in the laser + IVB group (baseline: 513 ± 126.29 vs. three months: 408.1 ± 95.28 ; $P < 0.001$) (Table 2).

There was no statistically significant change in CMT in the control group during the study compared with the baseline (baseline: 494.38 ± 130.7 vs. three months: 502.38 ± 145.88 ; $P = 0.64$) (Table 2).

Discussion

The present study revealed that using subthreshold diode micropulse laser photocoagulation with IVB could be an effective treatment modality for patients with refractory DME. Using subthreshold diode micropulse laser photocoagulation in combination with IVB can significantly reduce CMT and improve BCVA in patients with refractory DME.

The clinical effects of diode laser photocoagulation in the treatment of patients with DME are reported in different studies,^{14–16} but there are limited studies that used a subthreshold setting of this modality.^{17,18} All of these studies agree that diode laser can reduce CMT and improve or maintain VA.^{15,16} One study in 36 diabetic patients with CMT less than 600 μm evaluated the effects of subthreshold micropulse diode laser photocoagulation and revealed that this treatment method could significantly reduce CMT and maintain VA with minimal retinal damages.¹³ Another study on 95 eyes of 69 patients with significant DME evaluated the effects of subthreshold diode micropulse laser photocoagulation on improving VA. In this study, VA was enhanced or maintained in 85% of patients.¹⁹ Another study on 23 eyes of 16 patients

compared the effects of conventional organ laser therapy and subthreshold diode micropulse laser photocoagulation and showed that subthreshold laser could stabilize VA within three and six months after receiving treatment, and reduce CMT three months after intervention.²⁰

Most of the studies assessing the effects of subthreshold diode micropulse laser photocoagulation compared this method with other conventional laser methods, but not enough studies examined the impact of this method on different types of DME treatment, including intravitreal injections. As an effective treatment modality in refractory DME, IVB reduces CMT in these patients.²¹ One study divided patients with DME into four groups who received prompt focal/grid laser photocoagulation and sham injections, prompt laser and IVB, deferred laser and IVB, and prompt laser and intravitreal triamcinolone. This study revealed that using an immediate or deferred conventional standard laser photocoagulation with IVB can improve VA and OCT outcomes.²²

Subthreshold diode micropulse laser photocoagulation uses invisible infrared treatment beams²³ and is a method well tolerated by patients because it is painless. The macular edema areas can be treated aggressively due to reduced laser damage. This method has not shown complications that are accompanied by conventional laser treatment methods and minimizes the risk of chorioretinal scars.¹⁹ Due to reduced damage by subthreshold diode micropulse laser photocoagulation, this modality can be used as an early intervention in patients with DME and improve long-term vision prognosis.²⁴ Studies showed that using 810 nm diode laser pulses of short duration can affect retinal epithelial pigment with little effect on outer retina and choriocapillaris.^{25,26} Findings in this study were similar to those of previous studies.

The few discrepancies between studies are perhaps due to different inclusion/exclusion criteria used to select participants, and various methods were used in several studies to measure CMT in patients with DME. Also, in most previous studies, efficacy of micropulse laser photocoagulation as an initial treatment was compared with conventional laser photocoagulation, but in our study, micropulse laser photocoagulation was used in refractory case of DME. Another difference between the current study and others was side-by-side control design of our study that control the confounding factors.

The present study has its strengths and limitations. A strong point was its use of subthreshold diode micropulse laser photocoagulation in combination with IVB, as there are few studies that have evaluated the effects of this combination. Another strength was its method of dividing the eyes of patients such that each patient randomly had one eye in the first group that received laser therapy and IVB and another eye in the second group which received IVB alone. This randomization reduced the effects of confounding variables, including age and gender. One limitation of the study was its sample size which was small for generalizing the results to the general population. For further evaluation, comparing the effects of IVB alone, laser alone, and the combination of laser and IVB

is useful for assessing the exact impact of these two modalities on DME.

In conclusion, using subthreshold diode micropulse laser photocoagulation in combination with IVB can significantly reduce CMT and improve VA in patients with refractory DME.

References

- Lee DH, Kim YJ, Yoon YH. Minimally invasive microincision vitrectomy surgery with an intraoperative dexamethasone implant for refractory diabetic macular edema. *Ophthalmologica*. 2016;235(3):150–156.
- Hussain RM, Ciulla TA. Treatment strategies for refractory diabetic macular edema: switching anti-VEGF treatments, adopting corticosteroid-based treatments, and combination therapy. *Expert Opin Biol Ther*. 2016;16(3):365–374.
- Gutierrez-Benitez L, Millan E, Arias L, Garcia P, Cobos E, Caminal M. Dexamethasone intravitreal implants for diabetic macular edema refractory to ranibizumab monotherapy or combination therapy. *Arch Soc Esp Ophthalmol*. 2015;90(10):475–480.
- Bainbridge J. Refractory diabetic macular edema. *J Ophthalmic Vision Res*. 2010;5(3):143–144.
- Martidis A, Duker JS, Greenberg PB, et al. Intravitreal triamcinolone for refractory diabetic macular edema. *Ophthalmology*. 2002;109(5):920–927.
- Photocoagulation treatment of proliferative diabetic retinopathy: clinical application of diabetic retinopathy study (DRS) findings, DRS Report number 8 the diabetic Retinopathy study Research group. *Ophthalmology*. 1981;88(7):583–600.
- Otani T, Kishi S. A controlled study of vitrectomy for diabetic macular edema. *Am J Ophthalmol*. 2002;134(2):214–219.
- Jonas JB, Kreissig I, Söfker A, Degenring RF. Intravitreal injection of triamcinolone for diffuse diabetic macular edema. *Arch Ophthalmol*. 2003;121(1):57–61.
- Framme C, Brinkmann R, Birngruber R, Roeder J. Autofluorescence imaging after selective RPE laser treatment in macular diseases and clinical outcome: a pilot study. *Brit J Ophthalmol*. 2002;86(10):1099–1106.
- Pankratov MM. Pulsed delivery of laser energy in experimental thermal retinal photocoagulation. In: *Paper presented at: laser–tissue Interaction*. 1990.
- Othman IS, Eissa SA, Kotb MS, Sadek SH. Subthreshold diode-laser micropulse photocoagulation as a primary and secondary line of treatment in management of diabetic macular edema. *Clin Ophthalmol*. 2014;8:653–659.
- Elhamid AHA. Combined intravitreal dexamethasone implant and micropulse Yellow laser for treatment of anti-VEGF resistant diabetic macular edema. *Open Ophthalmol J*. 2017;11:164–172.
- Ohkoshi K, Yamaguchi T. Subthreshold micropulse diode laser photocoagulation for diabetic macular edema in Japanese patients. *Am J Ophthalmol*. 2010;149(1):133–139. e131.
- Akduman L, Olk RJ. Diode laser (810 nm) versus argon green (514 nm) modified grid photocoagulation for diffuse diabetic macular edema. *Ophthalmology*. 1997;104(9):1433–1441.
- Tewari H, Gupta V, Kumar A, Verma L. Efficacy of diode laser for managing diabetic macular oedema. *Acta Ophthalmol*. 1998;76(3):363–366.
- Gupta V, Gupta A, Kaur R, Narang S, Dogra MR. Efficacy of various laser wavelengths in the treatment of clinically significant macular edema in diabetics. *Ophthalmic Surg Lasers Imaging Retina*. 2001;32(5):397–405.
- Moorman C, Hamilton A. Clinical applications of the MicroPulse diode laser. *Eye*. 1999;13(2):145.
- Friberg TR, Karatza EC. The treatment of macular disease using a micropulsed and continuous wave 810-nm diode laser. *Ophthalmology*. 1997;104(12):2030–2038.
- Luttrull J, Musch D, Mainster M. Subthreshold diode micropulse photocoagulation for the treatment of clinically significant diabetic macular oedema. *Br J Ophthalmol*. 2005;89(1):74–80.
- Laursen M, Moeller F, Sander B, Sjoelie A. Subthreshold micropulse diode laser treatment in diabetic macular oedema. *Br J Ophthalmol*. 2004;88(9):1173–1179.
- Haritoglou C, Kook D, Neubauer A, et al. Intravitreal bevacizumab (Avastin) therapy for persistent diffuse diabetic macular edema. *Retina*. 2006;26(9):999–1005.
- Diabetic Retinopathy Clinical Research Network, Elman MJ, Aiello LP, Beck RW, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology*. 2010;117(6):1064–1077.
- Roeder J, Brinkmann R, Framme C, et al. Selective RPE laser treatment in macular diseases: clinical results. *Invest Ophthalmol Vis Sci*. 2001;42(4):S695.
- Bresnick GH. Diabetic maculopathy: a critical review highlighting diffuse macular edema. *Ophthalmology*. 1983;90(11):1301–1317.
- Kim S. The selective effect of micropulse diode laser upon the retina. *Invest Ophthalmol Vis Sci*. 1996;37:s779.
- Rutledge BK, Wallow IH, Poulsen GL. Sub-pigment epithelial membranes after photocoagulation for diabetic macular edema. *Arch Ophthalmol*. 1993;111(5):608–613.