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Original research

Comparison of subthreshold diode laser micropulse therapy versus conventional photocoagulation laser therapy as primary treatment of diabetic macular edema

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Abstract

Purpose: The aim of the present study was to investigate the effect of subthreshold diode laser micropulse (SDM) in comparison with conventional laser photocoagulation in the treatment of the diabetic macular edema (DME).

Methods: Sixty-eight eyes from 68 patients with clinically significant DME were divided randomly into two equal groups. In the first group, SDM photocoagulation was employed, while conventional laser photocoagulation was performed on the eyes of the second group. Central macular thickness (CMT), central macular volume (CMV), and best corrected visual acuity (BCVA) were measured before, 2, and 4 months after intervention, and the results were compared.

Results: The mean CMT was 357.3 and 354.8 microns before the treatment in Groups 1 and 2, respectively ($P = 0.85$), and decreased significantly to 344.3 and 349.8 after 4 months, respectively ($P = 0.012$ and $P = 0.049$). The changes in the central macular thickness was statistically higher in the first group ($P = 0.001$). The mean CMV significantly decreased in Group 1 ($P = 0.003$), but it was similar to pre-treatment in Group 2 after 4 months ($P = 0.31$). The BCVA improved significantly in Group 1 ($P < 0.001$), but it remained unchanged in Group 2 ($P = 0.38$).

Conclusions: In this study, SDM was more effective than conventional laser photocoagulation in reducing CMT and CMV and improving visual acuity in patients with DME.

Keywords: Diabetic macular edema; Subthreshold diode laser micropulse; Conventional laser photocoagulation

Introduction

Diabetic macular edema (DME) is one of the most important causes of visual deterioration in working-age patients who have diabetes mellitus.[1−3] DME was defined as retinal thickenings and/or edema threatening or involving the fovea that is visible by fundus examination or optical coherence tomography (OCT). When it involves the fovea, returning to the previous visual status is almost impossible.[4,5] DME is classified as focal and diffuse. The traditional treatment for macular edema had been laser photocoagulation, focal laser to induce photocoagulation of microaneurysms in focal DME, and grid pattern laser for diffuse type.[6]

Currently, intra-vitreal anti vascular endothelial growth factors (VEGF) injections with or without laser photocoagulation is the standard of care for patients with DME, and newer

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methods of laser such as subthreshold diode laser micropulse photocoagulation (SDM) are under investigation in an attempt to improve the efficacy while reducing the adverse events. The studies evaluating the safety and efficacy of SDM, in comparison with conventional laser therapy for macular edema, are limited.[3,7–9]

Our study was designed to compare the efficacy of SDM with conventional laser as a primary treatment of DME.

Methods

This single-blind, prospective, randomized, clinical trial was performed in the ophthalmology center of Feiz Hospital, Isfahan, Iran, between 2015 and 2016. The study was approved by the Ethics Committee of the Isfahan University of Medical Sciences and was registered in the Iranian Clinical Trial Registry (registration number IRCT2015122721890N2). We explained the aim of our study to the patients, and informed consent was obtained. Diabetic patients who were suffering from clinically significant macular edema (CSME)[10] and non-proliferative diabetic retinopathy (NPDR) in fundus exam were enrolled in the study. The inclusion criteria of our study were: the minimum best corrected visual acuity (BCVA) 20/200 or 1.00 Logarithm of the Minimal Angle of Resolution (LogMAR), the best corrected vision less than 20/25 or 0.10 LogMAR, and DME with the minimum central macular thickness (CMT) of 300 microns on OCT basis. The exclusion criteria were: monocular patients, DME with CMT more than 450 microns on the OCT, pregnant patients or pregnancy during the study, uncontrolled hypertension defined by systolic blood pressure (SBP) more than 160 mmHg and/or diastolic blood pressure (DBP) more than 110 mmHg, any history of intra-ocular surgery except uncomplicated phacoemulsification cataract surgery in past six months, any history of previous intra-ocular injections, any history of previous conventional laser photocoagulation of retina or subthreshold diode micropulse laser, previous history of glaucoma or ocular hypertension or an increase in intraocular pressure (IOP) during the study, macular diseases such as vitreo macular traction (VMT), epi retinal membrane (ERM), age-related macular degeneration (AMD), extensive non-capillary perfusion of macula in fluorescein angiography (FA), any visible scar in ophthalmic examination or fundus photograph after the study in the group treated with subthreshold diode micropulse laser, severe cataract not allowing the surgeon to observe the fundus, and lack of patient follow-up.

Sixty-eight patients were divided into two equal groups by block randomization. The first group was treated with SDM (Quantel-medical Co, Cournon-d'Auvergne, France), and the second group underwent the conventional macular laser photocoagulation (Quantel-medical Co, Cournon-d'Auvergne, France). In both groups, the wavelength of laser therapy was 810 nm.

All laser treatments were performed by an ophthalmologist (F.F). Prior to starting treatment with SDM, a test burn was performed in the nasal side to determine threshold power required for a visible tissue reaction for each patient. This test was done with 125 um spot, 200 ms exposure duration, and adjusted upward the power in the continuous wave (CW) emission mode until a light grayish visible burn was observed. When the threshold power of the patient achieved, the laser was changed to Micro-Pulse emission mode with 15% duty cycle, and the power was doubled with the same exposure duration.

SDM was conducted via dilated pupil as follows: adjustable power began from 1000 milli-joules with duration time of 300 μs, 15% duty cycle, and 75 to 125 micron spot size. All areas of clinically visible thickened and edematous retina in the macular area were treated excluding the foveal avascular zone (FAZ) with a safety margin of 100 microns around FAZ. Conventional laser photocoagulation was done via dilated pupil in the eyes of the second group as follows: adjustable power with 50–100 micron spot size, and 0.1 s duration time. Focal laser was applied in the distance of 500–3000 microns of the FAZ as well as on microvascular lesions with an exudative ring. In addition, grid laser was applied on clinically visible thickened retina in the macular areas excluding FAZ and a safety margin of 500-micron around the FAZ and 500-micron from the optic disc. For both groups, the laser treatment was performed once.

An ophthalmologist carried out laser treatment and the ophthalmic examination of the patients, including best corrected visual acuity (BCVA), slit lamp biomicroscopy, IOP measurement using Goldman applanation tonometer, and fundus examination after pupil dilation to confirm CSME and NPDR. These examinations and OCT were repeated in 2 and 4 months after the intervention, and the information of these evaluations was gathered in special sheets. Only one ophthalmologist performed all of the examinations and interventions for all of the patients. LogMAR was utilized to calculate BCVA. Cycloplegic refraction was done by autorefractometer (Topcon Medical system Inc. Tokyo, Japan) before the intervention and 2 and 4 months after the intervention.

The lens opacity was classified according to lens opacity classification III[11] as nuclear sclerosis, cortical cataract, or posterior subcapsular. After that, lenses were classified according to red reflex and physical examinations such as observing fundus, vascular branches, and head of optic nerve and especially surgeon experiments as mild, moderate, and severe. Very severe dense cataracts were excluded as explained above.

CMT (microns) was automatically calculated by OCT for all eyes (SD-OCT Heidelberg Engineering, Heidelberg, Germany). Baseline FA (Heidelberg Engineering Co, Heidelberg, Germany) was performed to evaluate areas of leakage and capillary non-perfusion. Fundus photographs (Engineering Heidelberg Co, Heidelberg, Germany) were taken before and at the end of the study to compare retinal changes.

After laser therapy, all patients were evaluated for the following possible complications: vitreous and intra-retinal hemorrhage, choroidal neovascularization, fovea burn, subretinal fibrosis, and retinal scar formation. The above-mentioned complications were assessed by fundus examination, OCT, and autofluorescence imaging.

Changes in CMT and CMV on the basis of OCT and BCVA (LogMAR), before and after intervention, were the primary outcomes. Statistical analysis was performed, using SPSS software (SPSS Inc, Chicago, IL, USA) version 23. The results with a level of $P < 0.05$ were considered statistically significant. Paired t test was used to compare the mean of measurements before and after treatment. Furthermore, student t-test was employed to analyze the quantitative data between the two groups. The chi-square test was used to compare the nominal qualitative data. Finally, the changes of quantitative variables between the two groups were analyzed by ANOVA with repeated measurement.

Results

34 patients with a mean age of 52.2 ± 6.7 years in the SDM group and 34 patients with a mean age of 53.7 ± 7.1 years in the conventional laser group were enrolled in the study. None of the eyes were excluded from the study during follow-up. Also, none of the patients needed cataract surgery during the study. Demographic and baseline characteristics of the patients are illustrated in Table 1. There was no significant difference concerning sex, age, the leakage pattern, the duration of the diabetes, the mean of IOP, the mean of cycloplegic refraction, and lens opacity between the two groups.

The mean and the standard deviation of BCVA, CMT, and CMV are summarized in Table 2. There was no significant difference between BCVA, CMT, and CMV before the treatment and 2 and 4 months after intervention between both groups ($P > 0.05$). In Group 1, treated with SDM, BCVA improved significantly after 4 months ($P < 0.001$), while this did not occur in Group 2 ($P = 0.38$). The mean changes of BCVA in Group 1 was −0.07 ± 0.01, and +0.02 ± 0.01 after 4 months in Group 2 ($P < 0.001$ and $P = 0.38$, respectively) (Table 2, Fig. 1).

Table 1
Demographic and general characteristics of the two groups.

Variables		SDM	CLP	P Value
Sex	**Male**	20 (58.8%)	19 (55.9%)	0.81
	Female	14 (41.2%)	15 (44.1%)	
Age	**The mean**	52.2 ± 6.7	53.7 ± 7.1	0.62
	<50 years old	14 (41.2%)	12 (35.3%)	
	≥50 years old	20 (58.8%)	22 (64.7%)	
Leakage pattern	**Focal**	22 (64.7%)	20 (58.8%)	0.62
	Diffuse	12 (35.3%)	14 (41.2%)	
The mean of disease duration (years)		18.1 ± 4.7	19.8 ± 4.4	0.13
The mean of IOP (mmHg)		17.94 ± 2.64	17.85 ± 3.06	0.9
The mean of refraction (Diopter)		−1.22 ± 0.44	−1.12 ± 0.62	0.44
Lens opacity	**Mild**	14 (41.2%)	13 (38.2%)	0.59
	Moderate	19 (55.9%)	18 (52.8%)	
	Severe	1 (2.9%)	3 (8.8%)	

SDM: subthreshold diode laser micropulse; CLP: conventional laser photocoagulation; IOP: intra-ocular pressure.

Table 2
The mean of best corrected visual acuity, central macular thickness, and central macular volume before and after the treatment in both groups.

Variables	Time	Treated groups		P Value
		SDM	CLP	
BCVA	Before intervention	0.59 ± 0.3	0.58 ± 0.32	0.91[a]
	After 2 months	0.58 ± 0.3	0.59 ± 0.32	0.9[a]
	After 4 months	0.52 ± 0.29	0.6 ± 0.33	0.29[a]
	P value	<0.001[b]	0.38[b]	0.015[c]
CMT	Before intervention	357.3 ± 56.4	354.8 ± 53.3	0.85[a]
	After 2 months	349.2 ± 57.4	353.3 ± 55.3	0.77[a]
	After 4 months	344.3 ± 59.5	349.8 ± 53.7	0.69[a]
	P value	0.012[b]	0.049[b]	0.001[c]
CMV	Before intervention	8.62 ± 1.24	8.89 ± 1.23	0.37[a]
	After 2 months	8.49 ± 1.19	8.87 ± 1.25	0.2[a]
	After 4 months	8.42 ± 1.23	8.84 ± 1.25	0.17[a]
	P value	0.003[b]	0.31[b]	0.001[c]

BCVA: best corrected visual acuity; CMT: central macular thickness; CMV: central macular volume; SDM: subthreshold diode laser micropulse; CLP: conventional laser photocoagulation.
[a] The difference between two groups analyzed by t-test.
[b] The difference within each group analyzed by ANOVA with repeated measurement test.
[c] The difference between two groups analyzed by ANCOVA with repeated measurement test.

Also in our study, the decrease of mean CMT in Group 1 was 13 ± 3.1 microns, and 5 ± 0.4 microns after 4 months in Group 2 ($P = 0.012$ and $P = 0.049$, respectively) (Table 2, Fig. 2). Although CMT in both groups decreased significantly after 4 months, its change was much higher in Group 1 (Table 2, Fig. 2).

The changes of central macular volume (CMV) after 4 months significantly declined in Group 1 ($P = 0.003$), while this decrease was not considerable Group 2 ($P = 0.31$). Interestingly, CMV before and during the study did not differ much between both groups (Table 2, Fig. 3). The complications of laser therapy, including vitreous and intra-retinal hemorrhage, choroidal neovascularization, fovea burn, and

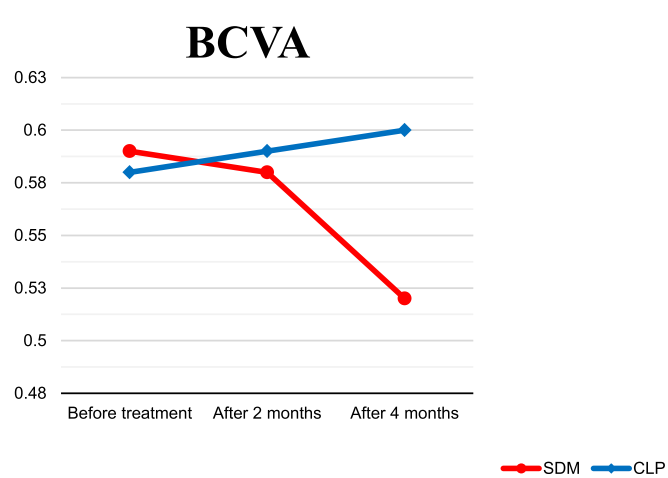

Fig. 1. The mean of BCVA (LogMAR) before the treatment and 2 and 4 months after it in Group 1 treated with subthreshold diode laser micropulse (SDM) versus Group 2 treated with conventional laser photocoagulation (CLP).

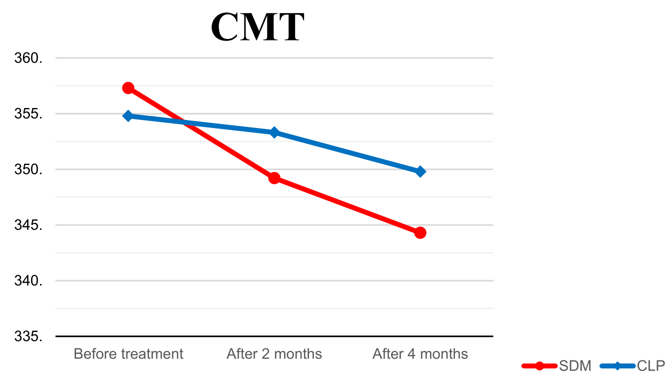

Fig. 2. The mean of central macular thickness (CMT) (microns) before the treatment and 2 and 4 months after it in Group 1 treated with subthreshold diode laser micropulse (SDM) versus Group 2 treated with conventional laser photocoagulation (CLP).

sub-retinal fibrosis were not observed in any case of either group. Although retinal scar formation was not noticed in Group 1, it was observed in all of the cases of Group 2.

Discussion

We studied the effect of SDM photocoagulation in comparison with conventional laser photocoagulation (focal or grid) on the reduction of the CMT and the CMV. Moreover, changes in the BCVA were compared with those of the two laser methods.

The important cause of retinal edema is serum leakage from abnormal decompensated endothelial cells, and the consequence is abnormal retinal vessels in patients with diabetic retinopathy. There are multiple therapeutic strategies for DME, including controlling blood sugar and hypertension and changing lifestyle as well as ocular therapies such as intravitreal corticosteroids or anti-vascular endothelia growth factors (anti-VEGF), laser treatment, and ultimately surgical pars plana vitrectomy in treating some complicated cases.[5,12–14] Laser light is absorbed by pigmented epithelium of the retina (RPE), leading to the destruction of the RPE and consequent diminution of retinal hypoxia due to the decrease in the retinal oxygen demand and diffusion of oxygen through the laser scar windows. Additionally, another hypothesis is related to the decrease in the VEGF from destructed RPE.[15,16] In the conventional method of laser photocoagulation, laser is applied to all of the leaking microaneurysms, using green or yellow wavelengths to treat focal form of DME, and grid pattern of laser is used to treat all areas of leakage in diffuse form of DME. In grid pattern laser, 500 microns are spared from the center of macula.[6] Nowadays, SDM is employed more by ophthalmologists owing to indistinguishable retinal scars during laser sessions or after completion of laser therapy and much fewer complications. SDM laser therapy is an invisible retinal phototherapy with no retinal damage by laser, and consequently, there is no inflammatory response and loss of functional retina. In addition, this method may increase heat sock protein 70 expression in the RPE without inducing cellular damage. SDM does not have any effects on neurosensory retina and is absorbed by RPE.[7,17–19] Cell function, especially for those cells in the pathologic environments like diabetes, is normalized by SDM; subsequently, cytokine production will be affected and inflammation response will cease.[20] In this method, the laser with 810 nm wavelength is applied. It is believed that SDM produces the same clinical effects as the conventional laser photocoagulation in destruction of the RPEs and decreasing retinal hypoxia.[17] SDM is tolerated well by patients because of invisible infrared wavelengths and lesser pain sensation during laser procedure.[21] Several studies have indicated a significant reduction of CSME on OCT basis or ophthalmic examination.[8,9,22–24] Furthermore, SDM has been utilized to treat proliferative diabetic retinopathy, central serous chorioretinopathy, macular edema due to branch retinal vein occlusion, and even glaucoma.[9,25–31] In addition, our study is the first one to evaluate the effect of SDM, in comparison with conventional laser photocoagulation, on the treatment of DME in Iranian patients. According to our results, SDM is more effective than conventional laser photocoagulation in decreasing CMT and CMV after 4 months in DME patients ($P = 0.001$). BCVA was established in both groups with a slight improvement in eyes treated with SDM after 4 months, but the difference between the two groups was significant ($P = 0.015$).

Luttrul et al showed a 24% reduction of foveal thickness after 3 months of SDM procedure.[24] One study similar to our study was performed in Oxford Eye Hospital that compared SDM with conventional green laser (CGL). That study did not demonstrate any significant differences between SDM and CGL in BCVA, retinal thickness, and contrast sensitivity.[9] Ohkoshi and Yamaguchi designed a study to evaluate the changes of visual acuity and macular edema after applying SDM to Japanese patients. They concluded that SDM can control the macular edema and maintain the visual acuity in diabetic patients with moderate DME; however, they did not

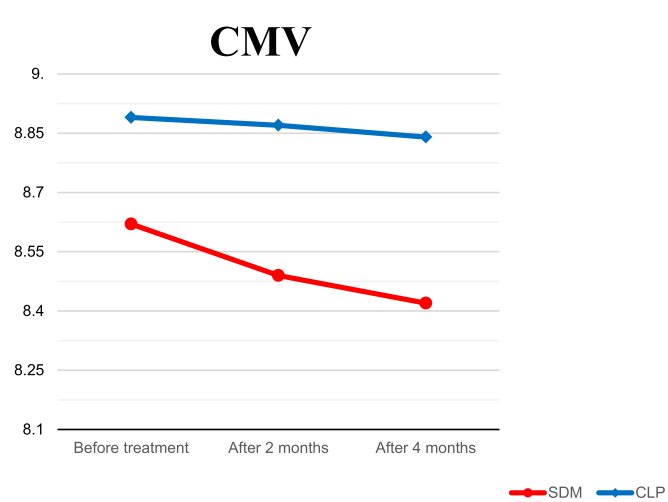

Fig. 3. The mean of central macular volume (CMV) (mm^3) before the treatment and 2 and 4 months after it in Group 1 treated with subthreshold diode laser micropulse (SDM) versus Group 2 treated with conventional laser photocoagulation (CLP).

compare SDM with other methods.[23] Another study was published in 2010, comparing microperimetry and fundus autofluorescent angiography (FAF) of diabetic patients treated with SDM versus conventional laser photocoagulation. The retinal sensitivity increased in the group treated with SDM and decreased in the other group. Moreover, SDM induced no changes in FAF. It was concluded that SDM is as effective as the conventional laser photocoagulation in treating CSME, except that it causes fewer scar formations and increases retinal sensitivity.[8] In an observational, pilot study performed in 2004, SDM was effective in improving or establishing visual acuity in 85% of the treated eyes, and macular edema decreased in 96% of the treated eyes.[21] In addition, anti VEGF was employed to treat DME. Several studies, such as READ-2, compared the effect of anti-VEGF, versus conventional laser photocoagulation, on treating DME. In READ-2, intra-vitreal Ranibizumab alone resulted in a 7-letter improvement after 6 months; however, laser or combination therapy (laser plus intra-vitreal Ranibizumab) had less favorable visual acuity improvement. After two years, although visual acuity did not differ between groups, macular thickness significantly improved in the Ranibizumab group.[13] In addition to the READ-2 study, a review including 1978 patients by Regnier et al showed significant superiority of anti-VEGF treatment compared with laser treatment. However, this review did not show significant superiority of ranibizumab in comparison with aflibercept.[14] Thus far, few studies have focused on the comparison of anti-VEGF and SDM. Therefore, more studies are required in this regard.

SDM is a new technique where laser is applied to RPE with better controlled photo thermal effect. The advantage of this method is tissue sparing in the location of laser and its surroundings. In conventional laser method, CW is used and, as a result, the temperature rises rapidly and leads to photothermal damage of neurosensory and inner retina. In SDM, the energy is delivered with a train of repetitive on- and off-periods. The time off is more than that of the "on-period" (The duration of the "on-period" and the "off-period" is 100–300 and 1700–1900 μs, respectively). Short "on" time period limits increase the power and temperature. During long time "off-period", the temperature decreases, and consequently, the thermal injury diminishes.[22,30]

A small sample size, short period of the follow-up, and no comparison with intra-vitreal anti-VEGF or corticosteroids were the major limitations of our study. We did not quantify the DME type based on the FA and OCT images. Also, we did not record the quantitative data for laser shots in this study. We recommend a study with a longer follow-up as well as a larger sample size and evaluation scotoma by using primetry to compare the effectiveness of these two laser treatment methods. In addition, it is worth performing a study to compare SDM with intra-vitreal anti-VEGF in order to measure the macular edema and visual acuity changes in patients with DME.

In conclusion, our results revealed that SDM was more effective than conventional laser photocoagulation in reducing CMT and CMV in patients with DME. Furthermore, the SDM treatment leads to no retinal scars during laser procedure. Therefore, it seems that SDM can be a good substitute for conventional laser photocoagulation in DME treatment if confirmed in future studies.

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