• Clinical Research •

Subthreshold micropulse laser versus intravitreal anti-VEGF for diabetic macular edema patients with relatively better visual acuity

Sezen Akkaya, Banu Açıkalın, Yusuf Emre Doğan, Fatih Çoban

Departmant of Ophthalmology, Sağlık Bilimleri University, FSM Training and Research Hospital, İstanbul 34752, Turkey

Correspondence to: Sezen Akkaya. Sağlık Bilimleri University, FSM Hospital, G Blok, Içerenköy, İstanbul 34752, Turkey. drsezenakkaya@gmail.com

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Abstract

● **AIM:** To compare the effects of yellow (577 nm) subthreshold micropulse laser (SML) and intravitreal (IV) anti-vascular endothelial growth factor (VEGF) treatment in patients with diabetic macular edema (DME) with relatively better visual acuity [best corrected visual acuity (BCVA) ≤0.15 logMAR].

● **METHODS:** The medical records of 76 eyes of 47 patients underwent IV (0.5 mg) anti-VEGF injection or SML for the DME with relatively better BCVA were reviewed. The IV group received three consecutive monthly IV anti-VEGF injections, then were retreated as needed. The laser treatment group was treated at baseline and 3mo, and then retreated at 6 and 9mo if needed. All participants were followed up for one year. The mean BCVA and mean central macular thickness (CMT) values changes over the follow-up were evaluated.

● **RESULTS:** Twenty-four and 23 patients were assigned to the SML and IV subgroups, respectively. The mean number of treatments was 3.64±0.76 in SML group and 5.85±1.38 in IV group (P<0.05). The subgroups were similar with regard to the mean BCVA score at baseline and at the 1st and 3rd months, but the score of SML group was better than that of IV group at the 6th, 9th, and 12th months (P<0.05). The decrease in the mean CMT values from baseline values was higher in SML group at the 6th, 9th, and 12th months (P<0.05).

● **CONCLUSION:** Yellow SML treatment is superior to IV anti-VEGF injection in DME patients with relatively better BCVA for increasing visual acuity and decreasing CMT at 6, 9, and 12mo. SML can be a good alternative first-line therapy for DME with BCVA ≤0.15 logMAR.

● **KEYWORDS:** diabetic macular edema; subthreshold micropulse laser; anti-VEGF injection

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INTRODUCTION

The most regularly observed microvascular complication related to diabetes is diabetic retinopathy (DR). The risk of this complication increases depending on how long the patient has had diabetes, generally up to 30%. Ten percent of the patients with this condition can develop severe visual impairment. Close to 7.5% of type 2 diabetes patients can develop diabetic macular edema (DME). In industrialized countries, this is the most common etiology of blindness for working-age adults. If left untreated, clinically severe DME can outcome in moderate visual loss in three years for 32% of the patients. This not only causes personal disability but also imposes a socioeconomic burden on the population[1-2].

Intravitreal (IV) anti-vascular endothelial growth factor (VEGF), a more frequently-used therapy than conventional macular laser treatments, is now the go-to treatment for DME of the central macula[3]. The benefit of IV in patients with DME has been identified in large multicenter trials[4-5]. Compared to control groups that received sham injections or laser treatment, patients treated with IV obtain sustained ETDRS letter gains by way of BCVA and reduced central retinal subfield thickness observed in optical coherence tomography (OCT)[6-7]. Prior to IV, the traditional treatment for DME was conventional laser photocoagulation (CLP)[8].The goal of CLP is to realize a burn of light intensity on zones of diffuse leakage or focal nonperfusion; however, this treatment can also result in side effects such as defects of visual field, epiretinal membranes and choroidal neovascularization because of retinal burning[9]. To reduce retinal damage, other wavelengths and techniques have been introduced, such as subthreshold micropulse laser (SML). SML delivers energy in short pulses; in this technique, the pulse envelope represents the duration that the pules are delivered. One envelope is splitted to 100 micropulses, each of which has an on time and an off time. To attain the therapeutic effect of laser photocoagulation, rather than the destruction

of photoreceptors, the stimulation of the retina pigment epithelium (RPE) alone may be all that is necessary[10]. SML treatments can be at wavelengths of 577 nm (yellow) or 810 nm (diode); however, as a characteristic of the micropulse technique focused at RPE cells, the 577 nm yellow laser has the superiority of better absorption by melanin compared to the 810 nm laser wavelength.

SML might seem like the ideal method of treatment for DME, given the lesser side effects and lower cost, as well as fewer patient visit requirements.

The goal of this study was to compare the effects of yellow SML photocoagulation with the effects of IV on patients with relatively better best corrected visual acuity (BCVA) ≤0.15 logarithm of the minimum angle of resolution (logMAR) and DME.

SUBJECTS AND METHODS

Ethical Approval This retrospective study was approved by the Scientific Research Commission of the FSM Hospital and was conducted in accordance with the principles of the Declaration of Helsinki. All patients were made aware of the study method, the expected outcome and the potential complications, and informed consent forms were obtained from them for the research.

The medical documents of all participants who received SML or IV (ranibizumab or aflibercept) injection for foveal center-involved DME and with a 0.7 or better BCVA from a Snellen chart at our clinic were reviewed. DME was detectioned by fundus examination, OCT, and fluorescein angiography (FA). A total of 47 participants aged between 31 and 69y; 22 females (46.8%) and 25 males (53.2%) completed the following research criteria. SML was implemented to 37 eyes of 24 patients at baseline and in the 3rd month and then applied in the 6th and 9th months, if necessary, while IV was applied to 39 eyes of 23 patients, three times a month, and then again if necessary.

Participants were included in the research if they presented with mild nonproliferative DR and DME, HgA1c≤6.5 with good metabolic control and BCVA between 0.15 and 0 according to the logMAR (20/20-20/28 with snellen) and if they were examined methodically during one-year follow-up.

Patients were excluded from the research if they had diseases that may cause macula edema or proliferative DR, had previously undergone intraocular surgeries within the past sixth months or were undergoing grid laser treatment or panretinal photocoagulation for any cause, had received IV treatments within the past 6mo, or had a history of cerebrovascular events. All patients were examined by doctor of internal medicine and were evaluated at baseline and in the 1st, 3rd, 6th, 9th, and 12th months with a complete ocular examination and OCT. BCVA was decided using a decimal visual acuity chart, and the result was exchanged a logMAR units. Spectral domain OCT (NIDEK RS-3000 Advance) tool used forcentral macular thickness (CMT) evaluations. OCT map was designed from six consecutive linear 6 mm scans oriented at intervals of 300 centered on the foveal zone.

The participants in the IV group initially received three monthly injections and were then retreated as required (PRN). The laser treatment group was treated on day 0 and in the 3rd month and was then retreated in the 6th and 9th months if required.

The retreatment rules for both therapy stylies were spongiform or cystoid macular edema in the OCT during the previous visit. SML (Supra Scan 577Y, Quantel Medical, Clermont-Ferrand, France) was applied with a spot diameter of 100 μm, a duration time of 0.2s and a duty cycle of 10 percent (0.2ms on and 0.8ms off). The power of laser was decided for each participant by making a threshold burn at the lowest energy needed to make a visible "test burn" with a continuous wave in a suitable region outside the vascular arcade without retinal edema. The laser power was subsequently used at half of that energy level in micropulse mode and applied in confluent spots to the whole zone of leakage, as assessed by the FA, including the foveal zone.

All injections were applied within operating room conditions. After cleaning the eye with 5 percent povidone iodine, a 30-gauge needle was inserted through the pars plana, and 0.5 mg of anti-VEGF was injected.

Statistical Analysis Statistical analysis was carried out using SPSS software version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed as the mean, standard deviation (SD), and frequency. The level of normal distribution of the parameters was assessed with a Shapiro-Wilks test. Student's *t*-test was used to compare two groups with normal distributions, and a Mann-Whitney *U* test was used to compare two groups without normal distributions. A paired sample *t*-test was used for the intragroup comparison of quantitative data with normal distribution, while a Wilcoxon signed-rank test was used for the intragroup comparison of parameters without normal distribution. A continuity (Yates) correction was used to compare qualitative data, and a *P*-value of <0.05 was considered statistically significant.

RESULTS

In terms of the rate of prevalence of mean age, gender distribution and initial mean visual acuity, no statistically significant difference was found between the two groups (*P*>0.05). The injection numbers of the IV group 5.85±1.38 were significantly higher than the laser numbers of the SML group 3.64±0.76 (*P*=0.001). The demographic characteristics of the patients can be found in Table 1.

BCVA (logMAR) were 0.096±0.06 and 0.091±0.05 at baseline; 0.104±0.08 and 0.090±0.07 in the 1st month; 0.087±0.09 and

0.105±0.08 in the 3rd month; 0.064±0.08 and 0.106±0.08 in the 6th month; 0.058±0.07 and 0.097±0.07 in the 9th month; and 0.054±0.07 and 0.095±0.08 in the 12th month, in the SML and IV groups, respectively. No statistically significant difference was identified between the groups in the mean BCVA score at baseline or in the 1st and 3rd months, although there were statistically significant differences in the 6th, 9th, and 12th months (P<0.05). In the SML group, the mean BCVA values in the 6th, 9th, and 12th months were statistically significantly better than in the IV group (P<0.05; Table 2). The change in the mean BCVA over time can be seen in Figure 1.

CMT values were 302.92±41.35 and 287.44±76.64 at baseline; 286.39±41.07 and 273.46±53.80 in the 1st month; 280.06±43.72 and 287.54±103.12 in the 3rd month; 275.56±38.98 and 278.03±61.07 in the 6th month; 268.03±32.62 and 276.51±53.67 in the 9th month; and 265.83±33.42 and 277.77±55.12 in the 12th month in the SML and IV group, respectively. There was no statistically significant difference between the groups in the mean CMT at baseline, 1st, 3rd, 6th, 9th, and 12th months but there was statistically significant difference in the mean CMT at 6th, 9th, and 12th months than baseline between the groups (P<0.05; Table 3). With that in mind, the decrease in the mean CMT in the IV group in the 1st, 3rd, 6th, 9th, and 12th months was not more statistically significant than the values obtained at baseline (P>0.05). Decreases in CMT were higher in the SML group in the 6th, 9th, and 12th months compared to the IV group, although not to a statistically significant degree (P>0.05; Table 4). After SML treatment we did not observe visible retinal changes in the color of the fundus photo, OCT images or FA. The following two photographs show OCT images of patients from two groups in the first year of treatment (Figures 2 and 3).

DISCUSSION

DME is the most common cause for low vision in DR patients. Many therapeutic choices are currently obtainable for the treatment of DME, including two of the most important choices, IV and SML. After IV was approved for the treatment of DME, traditional laser treatments were no longer considered suitable for DME treatment due to their possible side effects[11-12]. Regarding IV treatment of DME, investigative studies also showed its effectiveness in function and morphology.

The increase in BCVA and decrease in CMT after SML (+1.26 ETDRS letters and -74.9 μm) were greater compared to conventional laser (-0.29 ETDRS letters and -43.6 μm) therapy, although no study has used a control group with participants treated with IV[10].

After the RISE and RIDE research and the approval of ranibizumab, anti-VEGFs became the standard treatment method for DME[13]. As there are no trials comparing SML

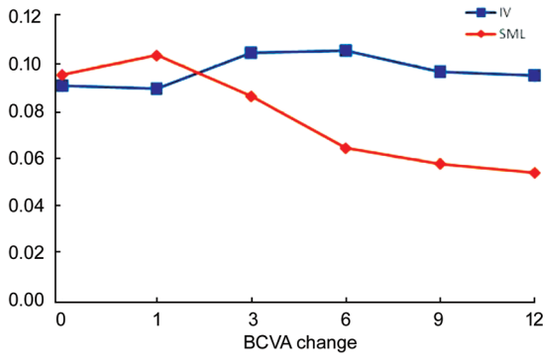

Figure 1 Mean change from baseline over time to month 12 in BCVA (logMAR).

Table 1 Assessment of general characteristics of patients in both groups mean±SD

Parameters	SML (n=24)	IV (n=23)	P
Age (y)	60.13±9.60	56.04±5.90	0.088[a]
No. of treatments (median)	3.64±0.76 (4)	5.85±1.38 (6)	0.001[b,d]
Gender, n (%)			0.564[c]
M	11 (45.83)	14 (54.17)	
F	13 (60.87)	9 (39.13)	

[a]Student's t-test; [b]Mann-Whitney U test; [c]Yates's continuity correction, [d]P<0.05. IV: Intravitreal anti-VEGF; SML: Subthreshold micropulse laser.

Table 2 Assessment of BCVA levels at baseline, 1st, 3rd, 6th, 9th, and 12th month for within group and between groups mean±SD

BCVA (logMAR)	SML	IV	[a]P
Baseline	0.096±0.06	0.091±0.05	0.686
1st month	0.104±0.08	0.090±0.07	0.510
3rd month	0.087±0.09	0.105±0.08	0.181
6th month	0.064±0.08[b]	0.106±0.08	0.009[c]
9th month	0.058±0.07[b]	0.097±0.07	0.014[c]
12th month	0.054±0.07[b]	0.095±0.08	0.016[c]

[a]Mann-Whitney U test; [b]P<0.05 *vs* baseline, Wilcoxon sign test; [c]P<0.05. BCVA: Best corrected visual acuity; IV: Intravitreal anti-VEGF; SML: Subthreshold micropulse laser.

Table 3 Assessment of CMT levels within and between groups at baseline, 1st, 3rd, 6th, 9th, and 12th month mean±SD, μm

CMT	SML	IV	[a]P
Baseline	302.92±41.35	287.44±76.64	0.218
1st month	286.39±41.07	273.46±53.80	0.326
3rd month	280.06±43.72	287.54±103.12	0.463
6th month	275.56±38.98[b]	278.03±61.07	0.328
9th month	268.03±32.62[b]	276.51±53.67	0.296
12th month	265.83±33.42[b]	277.77±55.12	0.270

[a]Student's t-test; [b]P<0.05 *vs* baseline, paired samples t-test. CMT: Central macular thickness; IV: Intravitreal anti-VEGF; SML: Subthreshold micropulse laser.

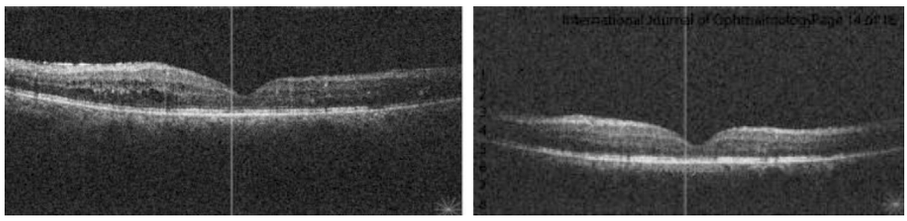

Figure 2 OCT images of one patient from SML group baseline and in the first year of treatment.

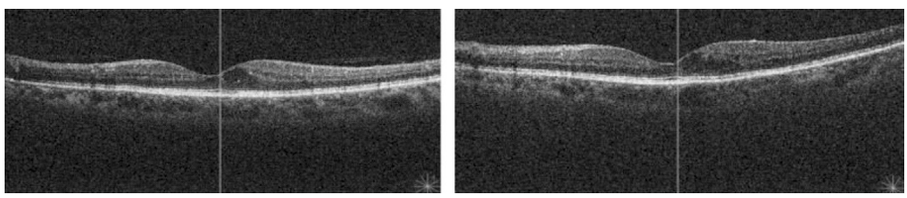

Figure 3 OCT images of one patient from IV group baseline and in the first year of treatment.

Table 4 Assessment of changes in CMT at 1st, 3rd, 6th, 9th, and 12th month compared to the initial values mean±SD, μm

CMT	SML	IV	[a]*P*
Difference between 1st month-baseline	-14.47±27.90	-13.97±79.65	0.517
Difference between 3rd month-baseline	-17.86±29.43	0.10±90.59	0.211
Difference between 6th month-baseline	-30.36±35.52	0.10±90.59	0.197
Difference between 9th month-baseline	-32.89±43.06	-10.92±85.71	0.170
Difference between 12th month-baseline	-39.08±46.84	-9.67±84.37	0.064

[a]Student's *t*-test. CMT: Central macular thickness; IV: Intravitreal anti-VEGF; SML: Subthreshold micropulse laser.

with IV, we still do not know under what circumstances SML therapy could be an alternative primary therapy for DME.

This is the first study in the literature that compares IV and SML therapy in DME patients suffering from relatively better visual acuity.

Nonetheless, SML may be considered an option for patients with insufficient response to IV or for those who are unable to continue treatment (due to compliance problems and high costs because of frequent visits for IV treatment). Therefore, SML is more affordable than ranibizumab and aflibercept. However, as is known, SML is used in very few centers, and patients have difficulty accessing them. In addition, long-term results have not yet been published.

There have been no studies that have reported complications after five SML sessions, so we could be considered the first to provide potentially better results from treatment with SML[12]. In the present study, the mean laser number was 3.64±0.76. RPE atrophy was not detected in any of our patients after one year, and no complications related to SML were encountered.

In the present research, we compared SML with IV in patients with relatively better visual acuity and CMT≤350 μm. We believe that it would be better to treat patients with relatively better visual acuity with SML to protect these patients from the serious risks of IV, such as endophthalmitis, IV hemorrhage and RPE atrophy[14].

Based on our clinical experience, SML is not very effective when the CMT is higher than 350 μm but is very effective in patients with relatively better visual acuity and whose CMT is lower than 350 μm. It is also highly effective in the early stages of DME, and furthermore, there are no related side effects, and treatment can be repeated at any given time.

IV did not increase the BCVA or decrease the CMT in this group, but only ensured that the BCVA and CMT levels remained stable. After the second month, we concluded that the minimal reduction in BCVA in the IV group may be affected psychologically by the patients wondering if they would be reinjected while looking at the level of vision.

We believe that VEGF levels may be lower in the vitreous for patients with relatively better visual acuity and low CMT values who are in the initial stages of DME compared to participants with low visual acuity and high CMT. This may be a reason why IV has less effect in such patients.

If visual acuity is low (BCVA≤20/40) and CMT is high (CMT≥350 μm), it may be more effective to begin treatment by reducing retinal thickness through IV and then to continue with SML, ultimately reducing the number of injections[15]. In this regard, starting with direct SML in cases with a low CMT and relatively better visual acuity would seem to be an appropriate treatment course, based on the findings of this study.

SML treatment for DME with high visual acuity was found to be better than IV in decreasing DME and increasing visual acuity in the 6th, 9th, and 12th months in our study.

Furthermore, if the patients in the present research had obtained monthly IV, the increase in visual acuity may have been bigger than in the SML group. However, a CATT study showed that a monthly IV injection and PRN protocol did not make any difference in vision levels up to 2y[16]. Due to the side effects associated with IV, we made three initial injections and then applied the PRN protocol, as our patients' BCVA scores were lower than ≤0.15 logMAR.

Inagaki *et al*[17] carried out SML on patients with BCVA levels over 20/40 and they found that visual acuity was protected for one year, and CMT decreased significantly in the 3rd, 6th, and 12th months. In their study the reasons of macular edema were branch retinal vein occlusion (BRVO). They concluded that SML carried out in participants with BCVA higher than 20/40 was effective in protecting visual acuity and decreasing macular edema[17], and some recent researches have shown that SML is an safe and effective alternative in patients with chronic central serous chorioretinopathy (CSC) and DME[18-20]. Although studies have shown the efficacy of SML for DME, CSC or BRVO, the parameters of treatment in these studies have differed. There have been no studies comparing different parameters of SML. Most authors standardized the SML power one by one for each patient. There is a high risk of insufficient treatment and failure of therapy because of SML is non visible. We used safe protocol rules, and we repeated three or four SML sessions, targeting the macular edema zones, including the fovea. We did not detect SML scars in any of the patients.

We used fundus photography, OCT, and FA at patient's follow-up. The absence of an auto fluorescence, a multifocal electroretinogram and microperimetry for a functional analysis can be considered as shortcomings of this study.

The other restrictions of our research are its retrospective nature, the absence of a control group, and long-term assessment of treatment results, and the relatively small sample size.

In conclusion, SML can be an alternative primary treatment for DME when CMT is lower than 350 μm and when BCVA≤0.15. In the present study, SML was shown to be superior to IV in such patients, with no side effects.

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