Efıcacy of Mıcropulse Laser In The Treatment of Dıabetıc Macular Edema

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Research Article

Keywords: Central Macular Thickness, Diabetic Macular Edema, Macular Volume, Micropulse Laser, Ranibizumab

Posted Date: November 29th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1096365/v1

Abstract

Purpose: In this study, we aimed to evaluate and compare the visual acuity, macular volume, central macular thickness, change in number of intravitreal ranibizumab injections with micropulse laser applications after loading dose of antiVEGF to DME patients.

Study Design: Retrospective study

Methods: This study was carried out on 97 patients (45 ranibizumab and 52 micropuls grid laser + ranibizumab) with diabetic macular edema patients who were followed in the Retina Unit. At the control visit after three loading ranibizumab injections administered once a month, micropuls grid laser was applied to one group and ranibizumab injection was continued PRN to both groups for an average of 9.27 ± 2.42 months and central macular thickness, macular volume and visual acuity were recorded.

Results: There was no significant difference between the groups in terms of gender, smoking and systemic diseases, initial central macular thickness, macular volume and visual acuity measurements ($p > 0.05$). Central macular thickness, macular volume and visual acuity values measured at the last follow-up of the patients were not significantly different between the groups ($p > 0.05$). The mean post-treatment injection requirement was 4.19 ± 1.01 for the ranibizumab with micropuls laser group and 5.53 ± 1.14 for the ranibizumab group. In the group treated with micropuls laser, statistically less number of intravitreal ranibizumab injections were needed ($p < 0.001$).

Conclusion:

Micropulse laser treatment after initial loading doses reduces the need for antiVEGF injections. Studies with the participation of more patients may help in the selection of treatment methods by comparing micropulse laser combined with different injection protocols.

Introduction

Macular edema is the most important cause of vision reduction in diabetic patients[1]. conventional laser treatment has been accepted as the main treatment modality in the Modified Early Treatment Diabetic Retinopathy Study (ETDRS) because it provided an increase in visual acuity and a decrease in the amount of edema in 50% of patients with diabetic macular edema (DME). Focal laser photocoagulation was recommended for areas with leakage due to microaneurysm, and grid pattern laser photocoagulation for areas with diffuse capillary leakage[2]. Conventional laser shows its effect by creating visible retinal pigment epithelium (RPE) and phoreceptor damage in ischemic and leaky areas[3].

After realizing the importance of Vascular Endothelial Growth Factor (VEGF) in DME pathophysiology, various prospective studies have proven the effectiveness of intravitreal anti-VEGF agents in DME treatment[4, 5]. Intravitreal anti-VEGF agents can achieve better visual acuity than laser photocoagulation treatment in eyes with DME and can be considered as the standard initial treatment for DME[2, 6, 7]. As

these treatments require repeated monthly injections high treatment costs occur and the possibility of injection-related complications increases[8]. In order to reduce the number of frequent injections, conventional laser and anti-VEGF treatments with different mechanisms of action have been combined to develop new treatment strategies and successful results have been achieved[9, 10].

Conventional laser is still considered an effective treatment method, but undesirable side effects may occur such as retinal scar enlargement, subretinal fibrosis and choroidal neovascularization development[11–13]. Subthreshold micropulse laser (SML) allows tissue cooling at the time of application by transmitting laser energy in an envelope with ON-OFF periods called duty cycle and is effective in DME treatment. Unlike conventional laser, SML does not cause visible retinal scar even on fundus autofluorescence (FAF) imaging, optical coherence tomography (OCT) and fundus fluorescence angiography (FFA) which are the most important advantages over conventional supratreshold lasers[14, 15].

In order to investigate the effectiveness of SML in DME treatment, patients who underwent SML in addition to ranibizumab injection treatment and who received only ranibizumab injection were retrospectively compared in a study with a limited number of patients[16]. The results of this study showed that the number of anti-VEGF injections was significantly reduced in the additional SML group, with no significant difference in anatomical and functional outcomes. In our study, we aimed to investigate the effectiveness of SML on DME treatment and its effects on the need for anti-VEGF injection in DME treatment with a larger number of cases.

Material And Method

The study was conducted retrospectively in the form of a patient card scan between May 2018 and January 2019 at Manisa Celal Bayar University Department of Ophthalmology Retina Unit. Ethical committe approval was obtained from our institution and the study was conducted under the tenets of Helsinki decleration (Ethics no: 25/06/2019/ 20.478.486).

The study included 45 patients who were treated for DME with anti VEGF- ranibizumab, 52 patients who received SML after intravitreal ranibizumab injection therapy for DME treatment.

The study excluded patients under 18 years of age, with a condition that could reduce visual acuity other than diabetic retinopathy (Patients with vein occlusion, age-related macular degeneration, epiretinal membrane, vitreomacular traction, amblyopia, optic neuropathy, glaucoma, corneal opacity, ocular trauma) and macular ischemia. Those who had ocular surgery or conventional retinal photocoagulation in 6 months before or during the treatment, and a history of focal laser treatment with conventional laser were not included in the study.

Best corrected visual acuity (BCVA), central macular thickness (CMT) and macular volumes (MV) measured by Cirrus HD OCT (Carl Zeiss Meditec, Germany) were recorded at the initial examination and

monthly controls of all patients. FFA imaging was performed with Visucam 524 (Carl Zeiss Meditec, Germany) and Heidelberg Spectralis HRA (Heidelberg Engineering, Heidelberg, Germany).

All patients received three monthly doses of loading intravitreal ranibizumab injections (0.5 mg / 0.05 mL; Lucentis, Genentech).

Group A was defined as patients who had a SMC 350μm at the third dose intravitreal intravitreal ranibizumab injection control visit, who underwent SML and received ranibizumab in monthly retinal controls when necessary. Group B was defined as patients who had a CMT ≤350μm at the control visit of the third dose of intravitreal ranibizumab injection and who received only PRN ranibizumab injection during monthly retinal controls. Age, gender, systemic disease histories, previous ocular surgery, and PRP treatments of both groups were recorded from follow-up cards. Total number of intravitreal ranibizumab injections at the end of the follow-up period were recorded.

In patients who underwent SML, a fundus image was obtained Visucam fundus camera. MPL (Supra Scan, Quantel Medical, Clermont-Ferrand, France) 577 nm was applied with an Area Centralis lens (Volk Optical, Mentor, OH, USA, 0.94 magnification) after topical anesthesia with proparacaine hydrochloride (Alcaine). Laser parameters were spot diameter 165 μm, 5% DC (duty cycle), 200 ms duration. Laser power was first increased up to the power to create a vague spot in titration spots in the retinal area in the two disc periphery of the posterior pole, then power was reduced to half, and the automatic grid pattern in laser machine was applied. If necessary additional focal laser was applied to the areas with increased retinal thickness in OCT imaging.

The compliance of continuous numerical data to normal distribution was decided by evaluating the Shapiro-Wilk test and histogram. Student t test was used for comparisons in two independent groups for continuous numerical variables conforming to normal distribution, ANOVA for repeated measures and ANOVA for two-factor repetitive measurements were used for dependent group comparisons with more than two groups, and their mean values were compared. In cases where normal distribution conditions were not met, Mann Whitney U test was used to compare two independent groups, and Friedman test was used to compare multiple measurements, and median values were compared. In the analysis of the data, Statistical Package of social science (SPSS, Chicago, inc, USA version 21.0) was used in analysis of the collected data and a statistically p value of <0.05 was considered significant.

Results

The study evaluated 97 eyes of 97 patients meeting the inclusion criteria and they were randomly assigned to receive laser or not (Group A; 52, Group B; 45 patients). The demographic characteristics and medical histories of hypertension, ophthalmological examination information and past ophthalmic treatments of both groups were similar (Table 1,2).

Table 1
Demographic characteristics of both groups and histories of hypertension disease

	Group				
	Anti VEGF and micropulse (Group A) (n = 52)		Anti VEGF (Group B) (n = 45)		
	Number	Percent	Number	Percent	p
Gender					
Male	28	53.8	20	44.4	0.36
Woman	24	46.2	25	55.6	
Systemic illness					
HT	23	44.2	21	46.7	
Age (Mean ± SD)	62.4 ± 7.6		61.6 ± 6.7		0.58

Table 2
Ophthalmological examination findings and treatment histories of both groups

	Group				
	Anti VEGF and micropulse (n =52)		Anti VEGF (n = 45)		
	Number	Percent	Number	Percent	p
Pseudofak	9	17.3	9	20,0	
PPV	0	0.0	1	2.2	
PRP	11	21.2	13	28.9	0.38
Anti-VEGF Injection history	6	11.5	8	17.8	0.38

* PPV = Pars Plana Vitrectomy

* PRP = Panretinal Photocoagulation

Initial CMT in Group A was mean 426.67 ± 96.90 µm and 406.00 ± 130.40 µm in Group B, initial MV mean 12.90 ± 1.42 mm3 in Group A and 12.25 ± 1.44 mm3 in Group B, the mean baseline BCVA was 0.43 ± 0.23 (Snellen acuity) in Group A and 0.41 ± 0.25 in Group B. There is no statistically significant difference between the groups in terms of baseline CMT, MV and BCVA measurements (p> 0.05)

The mean follow-up period for Group A was 9.25 ± 2.55 months, and for Group B was 9.29 ± 2.29 months. There was no significant difference between the groups (p = 0.44)

At the last examination of the patients, mean CMT in Group A was 311.31 ± 35.77μm, in Group B 304.25 ± 45.53μm (p = 0.23). Macular volume in Group A was 10.80 ± 0, 44mm3, in Group B 11.00 ± 0.60mm3 (p = 0.23), in BCVA Group A 0.71 ± 0.06, in Group B 0.69 ± 0.17 (p = 0.40).

There was no statistically significant difference between the groups in terms of CMT, MV and BCVA at their last examination (p> 0.05). CMT, BCVA and MV changes of the groups are indicated in Chart 1, Chart 2 and Chart 3, respectively. The mean post-laser intravitreal injection need was 4.19 ± 1.01 for Group A and 5.53 ± 1.14 for Group B (p <0.001). In the micropulse laser applied group, the number of intravitreal ranibizumab injections decreased significantly.

Discussion

In 2018, the first study by Moisseiev et al on the need for anti-VEGF injection in the treatment of DME and the effect of micropulse laser therapy included 38 eyes of 38 patients. It was in the same design as our study. They followed the SML group for an average of 19.1 months, and the anti-VEGF group for 23.2 months. It was found that visual acuity increased in both groups, and CMT decreased significantly in both groups, more in the anti-VEGF group. At the end of the treatment they stated that the micropulse laser group needed statistically significantly less injections as in our study (2.6 ± 3.3 vs 9.3 ± 5.1, p <0.001)[17].

Mansouri et al. Examined the effectiveness of micropulse treatment in DME patients with a central macular thickness value above and below 400μm in 2014. They found that micropulse laser treatment gave more positive results in the group with a central macular thickness below 400μm (CMT and BCVA). In addition, They were determined that while additional anti-VEGF treatment was needed in the other group, it was not in this group, which central macular thickness below 400 μm. In our study, patients with a CMT of 350μm or less after loading ranibizumab treatment for both groups were included, thus we aimed to prevent inadequate treatment disputes that may occur due to a high CMT for the laser group[18].

In 2019, Khattab et al. compared the efficacy of intravitreal aflibercept injections and treatments in DME treatment in 54 eyes. They applied only aflibercept injection (27 eyes) to one group, and a combination of aflibercept injection and MPL (27 eyes) to the other group, followed prospectively for 18 months. They reported that the CMT values at the end of 18 months decreased significantly in both groups, but there was no significant difference between the groups, likewise, the BCVA increased significantly in both groups, and there was no difference between the groups. Contrast sensitivity did not change significantly. They reported that the need for injection was significantly less in the MPL group compared to the other group (4.1 ± 1.1 vs 7.3 ± 1.1, p <0.005). There were no ocular or systematic side effects after either method[19].

In 2018, Wu et al. In a meta-analysis compiling 18 studies, they evaluated the results of MPL, ranibizumab injection and conventional laser treatments. They stated that the combination of ranibizumab and conventional laser therapy was generally more effective in terms of visual acuity results than using only micropulse therapy. There was no difference in terms of results in the comparison of conventional and micropulse lasers[20]. Considering the preferable features of MPL treatment, such as being repeatable, and non-damaging to RPE and photoreceptors, it has been suggested to consider this treatment modality as an important option in DME treatment[21].

Ranibizumab injection and micropulse laser applications applied to patients diagnosed with diabetic macular edema were performed to evaluate and compare BCVA, MV and CMT measurements and injection needs before and during follow-up. It was found that the total number of injections was lower in the group in which the micropulse laser was applied after the loading ranibizumab treatment compared to the anti-VEGF group (Group A 4.19. ± 1.01, Group B 5.53 ± 1.14), while other variables were found to be similar between the groups.

In our study, There was no significant difference between the groups in terms of gender, age, systemic hypertension, eye diseases and previous operations. When the number of patients was compared with similar studies in the literature, it has a high sample size of 97 cases [14, 17–19, 22]. We think that these situations increase the reliability of our study. Another important situation is that the values recorded before the treatment in the patient groups whose treatment results are evaluated are similar between the groups. This situation supports our hypothesis that our results are developed on a treatment-specific basis. We encountered difficulties in the follow-up of the patients, longer follow-up periods may provide more meaningful information.

In conclusion, additional micropulse laser treatment applied together with anti-VEGF injections in DME treatment may reduce the number of anti-VEGF injections. More comprehensive studies may support widespread use of micropulse laser applications in the standard treatment algorithm for DME treatment.

Declarations

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Figures

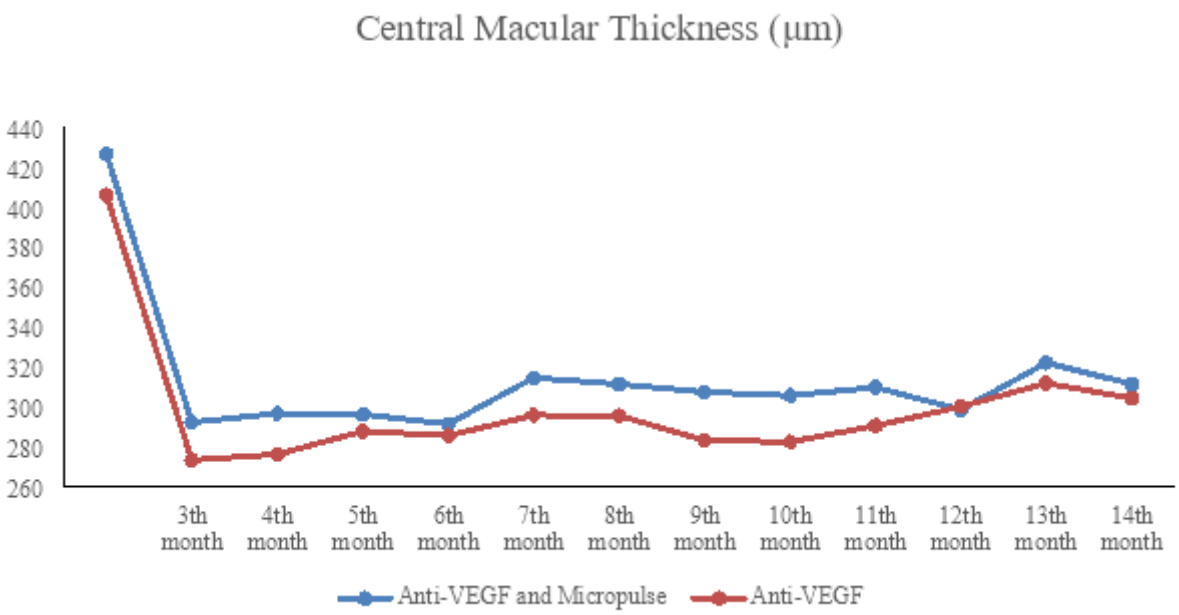

Figure 1

The initial central macular thickness values of the groups and their changes during the treatment process

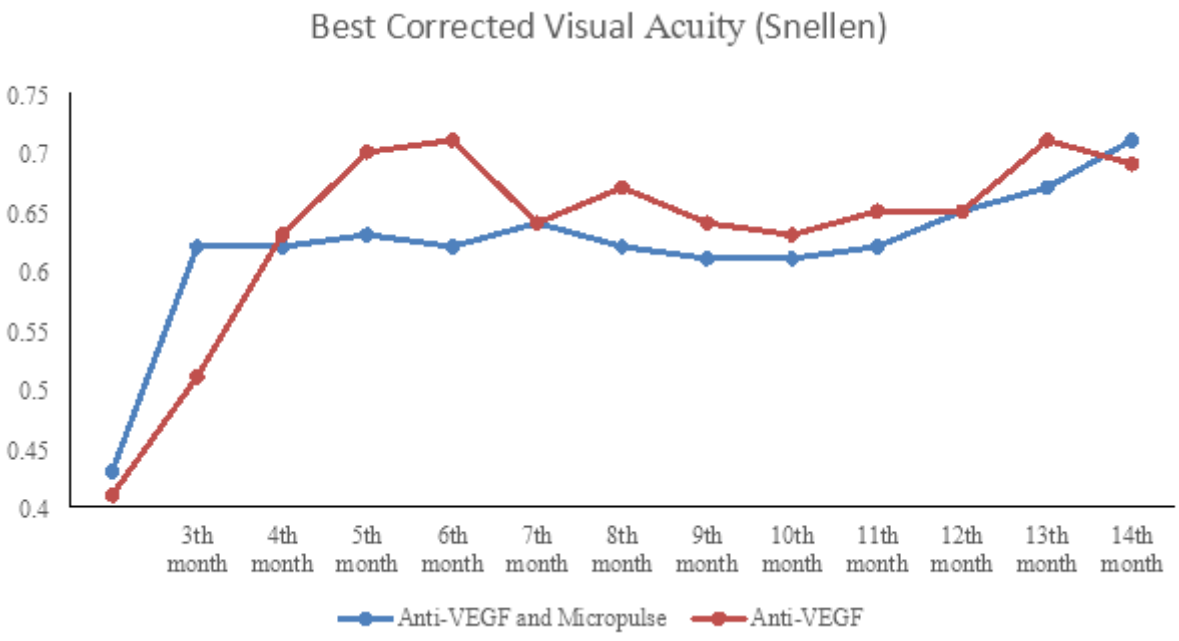

Figure 2

The initial visual acuity values of the groups and their changes during the treatment process

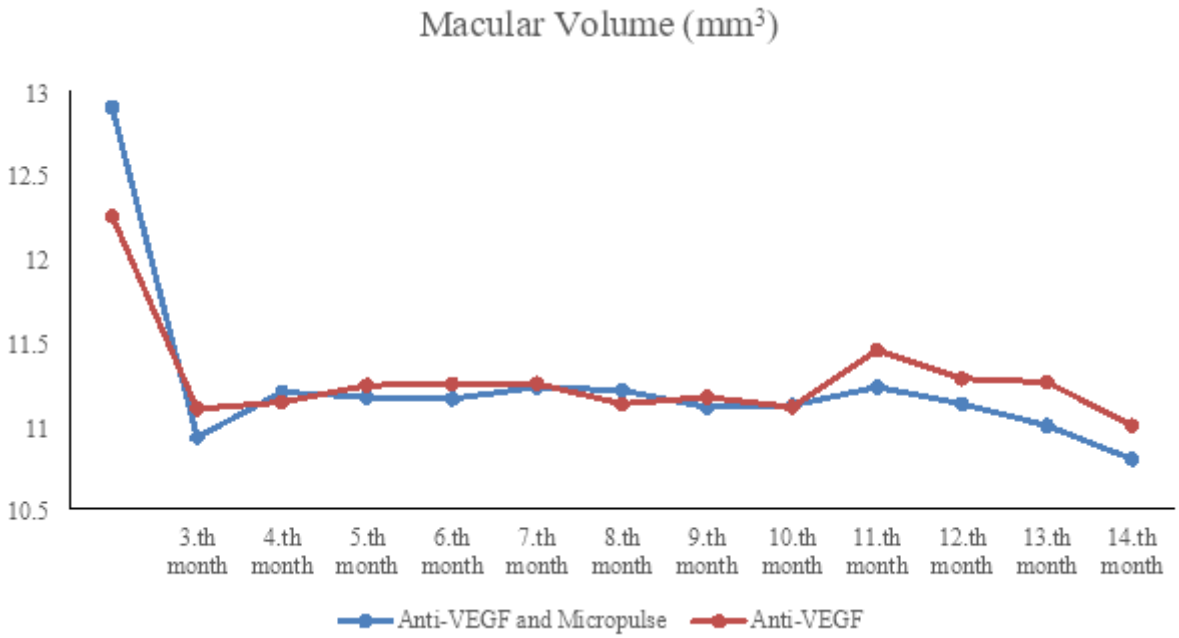

Figure 3

The initial macular volume values of the groups and their changes during the treatment