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Comparison of ranibizumab and subthreshold micropulse laser in treatment of macular edema secondary to branch retinal vein occlusion

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Abstract

Purpose: To compare the effects of intravitreal ranibizumab injection and yellow (577 nm) subthreshold micropulse laser treatment in patients with macular edema following non-ischemic branch retinal vein occlusion.

Methods: The medical records of 51 patients who underwent intravitreal ranibizumab (0.5 mg) injection or subthreshold micropulse laser for the treatment of macular edema due to branch retinal vein occlusion were retrospectively reviewed. Subthreshold micropulse laser was administered with a 10% duty cycle, 100 µm spot diameter, 200 ms exposure time. The patients received an injection or laser treatment at baseline and were, then, retreated as needed and were followed for 12 months. The mean best corrected visual acuity changes over the follow-up and the decrease in the mean central macular thickness were evaluated.

Results: A total of 27 and 24 patients were assigned to intravitreal ranibizumab and subthreshold micropulse laser subgroups, respectively. The mean number of treatment was 3.81 of intravitreal ranibizumab group and 1.5 of subthreshold micropulse laser group ($p < 0.05$). The subgroups were similar with regard to the mean score of best corrected visual acuity at baseline, at 1, 6, and 12 months ($p > 0.05$). The decrease in the mean central macular thickness was significant in both intravitreal ranibizumab and subthreshold micropulse laser groups at 1, 6, and 12 months than that of values at baseline ($p < 0.05$). No new ocular or systemic adverse events were observed.

Conclusion: Our study results showed that intravitreal ranibizumab or yellow subthreshold micropulse laser treatment for macular edema due to branch retinal vein occlusion was not found to be superior to each other for reducing macular thickness and increasing visual acuity for 1-year period. Based on these results, subthreshold micropulse laser may be a useful alternative approach in the treatment of macular edema secondary to branch retinal vein occlusion.

Keywords

Branch retinal vein occlusion, macular edema, ranibizumab, subthreshold micropulse laser

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Introduction

Retinal vein occlusion is the second most common retinal vascular disease after diabetic retinopathy.[1] Branch retinal venous occlusion (BRVO) occurs with the occlusion of one of the branches of the retinal vein. The occlusion occurs mostly at the arteriovenous crossings and is more frequent in upper temporal retinal veins. The main cause of reducing of visual acuity (VA) in BRVO is macular edema

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(ME).[2] ME causes photoreceptor damage as long as it persists; even if the edema is progressively reduced, the VA is reduced. The main goal of the treatment is to reduce the photoreceptor damage by decreasing the duration of edema.

Retinal vein occlusion causes an increase in the vascular endothelial growth factor (VEGF) levels in the vitreous. The VEGF has complex interactions with the immune system; it produces local inflammation, stimulates increased vascular permeability, and induces vascular endothelial cell proliferation.[2–4] Several studies have shown that there is a decrease in macular thickness and an increase in VA in ME due to BRVO following the intravitreal anti-VEGF injection.[5–7] Ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA, USA) is the first VEGF inhibitor to be evaluated in large-scale, randomized, controlled trials for BRVO. It is a humanized, affinity-matured VEGF antibody fragment that neutralizes all isoforms of VEGF-A and it is approved by the US Food and Drug Administration (FDA) for the treatment of ME secondary to BRVO.

In the Branch Vein Occlusion Study, the most comprehensive prospective study, it was reported that grid-pattern argon laser photocoagulation therapy was shown to reduce ME and increase the VA.[2] This study was limited because it has no optic cohorence tomography (OCT) data to show the anatomical response. Possible irreversible paracentral retinal tissue damage and parafoveal scotomas may develop due to laser photocoagulation to the macula. The endpoint of conventional laser photocoagulation (CLP) at the threshold level is a visible whitening of the retina due to thermal damage of the retinal pigment epithelium and the inner retina. In contrast to the CLP, the therapeutic effect of the subthreshold micropulse laser (SML) is not accompanied by thermal retinal damage. Scarring seems not to be necessary to achieve a therapeutic effect. It may be the stimulation of the retinal pigment epithelium (RPE) alone and not the destroying of the photoreceptors that is needed to reach a therapeutic effect of laser photocoagulation.[7] Subthreshold laser technologies use a series of shorter pulses rather than a short continuous laser delivery, allowing us to better preserve the retina by avoiding visible scarring either during or after treatment. The laser energy stimulates the RPE, which leads to repair of the inner blood retinal barrier.[8] Micropulse laser therapy is a subthreshold laser application method. In micropulse mode, the laser energy is delivered in short pulses. The whole pulse duration is called a pulse envelope, which is divided into 100 micropulses and each micropulse has active on time and inactive off time with a ratio depending on the duty cycle (the ratio between the on time and the whole micropulse on and off time). The "off" time is important since here the originated heat can cool down. SML treatment is a less invasive procedure for RPE than CLP, and also it has minimal effect on neurosensorial retina.[8–11]

The SML protocols can be at wavelength of 810 nm (diode) or 577 nm (yellow). Both of them are negligibly absorbed by xanthophyll pigment, potentially allowing for treatment close to the fovea. 577 nm yellow laser has the advantage of being better absorbed by melanin than the 810 nm laser wavelength, a characteristic that is theoretically suited to the micropulse technique aimed at RPE cells. A potential disadvantage of the 810-nm laser is a possible sensation of pain during treatment with a diode laser due to its deep penetration. Micropulse laser is used for particularly diabetic macular edema (DME), ME due to retinal venous occlusions, and central serous chorioretinopathy (CSC).[12,13] The aim of this study was to compare the effects of intravitreal ranibizumab (IVR) and yellow SML on eyes with ME due to BRVO.

Methods

This retrospective study was approved by the Scientific Research Commission of Fatih Sultan Mehmet Training and Research Hospital and conducted in accordance with the principles of the Declaration of Helsinki. The medical records of all patients who underwent SML or IVR injection for foveal center-involved ME following BRVO at our clinic between February 2011 and May 2016 were reviewed. ME due to BRVO was diagnosed by fundus examination, OCT and fluorescein angiography (FA) workups. A total of 51 patients, aged between 31 and 81 years, composed of 32 males (62.7%) and 19 females (37.3%) completing the following study criteria. The SML was applied to 24 patients, while IVR was applied to 27 patients. Among the patients who were admitted due to ME secondary to BRVO at least 3 months from the time of the occlusive event, those with central macular thickness (CMT) of 250 µ and above, those whose best corrected visual acuity (BCVA) was between 0.22 and 1 according to the logarithm of the minimum angle of resolution (LogMAR), and those examined regularly during 1-year follow-up were included in the study.

Patients with disease which may cause ME other than BRVO, patients who underwent intraocular surgery within the past 6 months, larger than 5 disc diameter of ischemic areas in FA, neovascularization or rubeosis, grid laser therapy or panretinal photocoagulation for any reason, any intravitreal injections within the past 6 months, geographic atrophy, and choroidal neovascular membrane that may affect VA results, fluorescein allergy, those with a history of cerebrovascular events, or uncontrolled hypertension were excluded from the study.

A detailed medical history was obtained from each patient included in the study. All patients were consulted to the department of internal medicine following the assessment of their routine laboratory results. Patients were evaluated at baseline, at 1 week, and 1, 2, 3, 6, 9, and 12 months with a complete eye examination and OCT. The BCVA was determined using a decimal VA chart, and the decimal

Table 1. Demographic and clinical characteristics of patient groups.

	IVR (n = 27)	SML (n = 24)	p
	Mean ± SD	Mean ± SD	
Age	64.7 ± 13.87	65.33 ± 11.82	0.863[a]
Number of treatments (median)	3.81 ± 1.11 (4)	1.5 ± 0.51 (1.5)	0.001[b,*]
Sex, n (%)			
Men	18 (66.7)	14 (58.3)	0.746[c]
Women	9 (33.3)	10 (41.7)	
Diabetes, n (%)			
Yes	15 (55.6)	12 (50)	0.908[c]
No	12 (44.4)	12 (50)	
Hypertension, *n* (%)			
Yes	17 (63)	15 (62.5)	1.000[c]
No	10 (37)	9 (37.5)	

IVR: intravitreal ranibizumab; SML: subthreshold micropulse laser.
[a]Student's t test.
[b]Mann–Whitney U test.
[c]Yates's continuity correction.
*$p < 0.05$.

VA was converted to the LogMAR units. Measurement of intraocular pressure, anterior segment, and dilated fundus examination was performed by biomicroscopy. CMT measurements were performed with spectral domain OCT (NIDEK RS-3000 Advance) device. The OCT map was created from six consecutive linear 6 mm scans oriented at intervals of 30° and centered on the foveal region. The FA was performed to confirm diffuse dye leakage and rule out focal capillary nonperfusion at baseline and at 3rd, 6th, and 12th month.

All patients were informed about the treatment method, its expected effects, and possible complications, and informed consent forms were obtained. The patients received an initial injection or laser treatment on day 0 and were then retreated as needed Pro re nata (PRN).

Retreatment criteria for both treatment modalities were ≥250 µ of CMT or decreased vision, compared to the last visit. The patients who needed retreatment were examined again at the same time points described above.

All injections were performed under operating room conditions. Briefly, topical anesthetic drops were instilled, a lid speculum was inserted, and cleaning of the injection site with 5% povidone iodine, a 30-gauge needle was inserted through the pars plana and 0.5 mg of ranibizumab was injected. Immediately after injection, perfusion of the retinal artery was assessed and tobramycin (3%) was instilled.

A 577 nm yellow laser system (Supra Scan 577Y; Quantel Medical, Clermont-Ferrand, France) was used in subthreshold micropulse mode in the outpatient condition. Fundus image was obtained by placing Area Centralis lens (Volk Optical, Mentor, OH, USA; 1.06× image magnification). With a spot diameter of 100 µm, a duty cycle of 10% (0.2 ms on and 1.8 ms off), and a duration time of 0.2 s, the laser power was determined for each patient by creating a threshold burn with the lowest energy required to make a visible "test burn" with continuous wave in an appropriate area outside the vascular arcade without retinal edema. The laser power subsequently was used at half of that energy level in micropulse mode and applied confluent spots to the whole area of leakage as assessed by the FA including the foveal center.

Statistical analysis was performed using the SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). The normal distribution of parameters was assessed by the Shapiro–Wilk test. The descriptive statistics were expressed in mean, standard deviation (SD), and frequency. Student's t test was used to compare two groups with normal distribution, whereas the Mann–Whitney U test was used to compare two groups without normal distribution. The paired sample t test was used for intra-group comparison of quantitative data with normal distribution, while the Wilcoxon signed-rank test was used for intra-group comparison of parameters without normal distribution. The continuity (Yates) correction was used to compare qualitative data. A p value of <0.05 was considered statistically significant.

Results

There was no statistically significant difference in the mean age, gender distribution, diabetes, and hypertension between two groups ($p > 0.05$). However, the number of injections in the IVR group was statistically significantly higher than the number of laser applications used in the SML group ($p < 0.05$). The demographic characteristics of the patients are shown in Table 1.

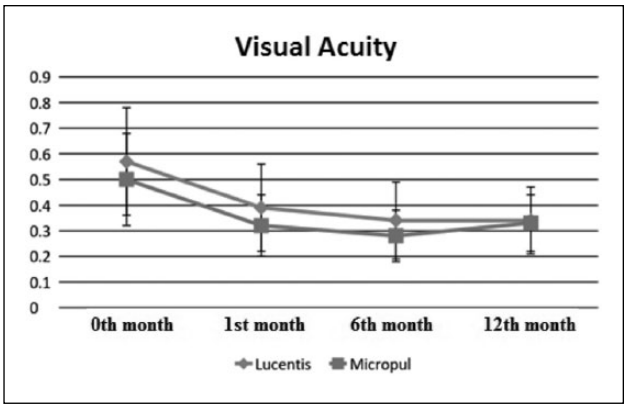

Figure 1. Mean change in best corrected visual acuity (LogMAR) from baseline to 12th month.

Table 2. BCVA levels at baseline, and at 1st, 6th, and 12th month (intra- and inter-group analyses).

BCVA (LogMAR)	IVR	SML	p[a]
	Mean ± SD (median)	Mean ± SD (median)	
Baseline	0.57 ± 0.21 (0.6)	0.5 ± 0.18 (0.5)	0.112
1st month	0.39 ± 0.17 (0.4)	0.32 ± 0.12 (0.3)	0.151
6th month	0.34 ± 0.15 (0.3)	0.28 ± 0.1 (0.3)	0.111
12th month	0.34 ± 0.13 (0.3)	0.33 ± 0.11 (0.4)	0.829
Baseline–1st month p[b]	0.001*	0.001*	
Baseline–6th month p[b]	0.001*	0.001*	
Baseline–12th month p[b]	0.001*	0.001*	

BCVA: best corrected visual acuity; IVR: intravitreal ranibizumab; SML: subthreshold micropulse laser.
[a]Mann–Whitney U test.
[b]Wilcoxon signed-rank test.
*$p < 0.05$.

The mean BCVA was 0.57±0.21 and 0.5±0.18 at baseline, 0.39±0.17 and 0.32±0.12 at 1st month, 0.34±0.15 and 0.28±0.1 at 6th month, 0.34±0.13 and 0.33±0.11 at 12th month in the IVR and SML groups, respectively. There was no statistically significant difference between the groups in terms of the mean BCVA scores at baseline and at 1st, 6th, and 12th month ($p > 0.05$). In both groups, the increase in the mean BCVA values at the 1st, 6th, and 12th months were statistically significant compared to the mean BCVA values at baseline ($p < 0.05$). (Table 2) The change of the mean BCVA over time is shown in Figure 1.

In addition, the mean CMT values were 519.59±127.36 and 495.83±97.74 at baseline, 300.44±61.93 and 323.58±61.83 at 1st month, 265.67±29.93 and 296.5±52.09 at 6th month, 286.37±29.68 and 317.17±37.42 at 12th month in the IVR and SML groups, respectively. There was no statistically significant difference between the groups in terms of the mean CMT at baseline and 1st month ($p > 0.05$). However, the mean CMT of the IVR group at 6th and 12th months was found to be statistically significantly lower than that of the SML group ($p < 0.05$). Also, the decrease in the mean CMT in both IVR and SML groups at 1st, 6th, and 12th month was statistically significant than that of values at baseline ($p < 0.05$) (Table 3). There was no statistically significant difference between the groups in terms of decrease in the CMT at 1st, 6th, and 12th month ($p > 0.05$) (Table 4). The change of the mean CMT over time is shown in Figure 2.

In the present study, we observed no visible retinal changes after the SML treatment on color fundus, OCT images, and FA.

Discussion

In our study, IVR or SML treatment for ME due to BRVO were not found superior to each other for reducing ME and increasing VA for 1-year period. The protocol of our study was determined according to the protocol PRN. Collateral development in vein occlusions is an adaptation to provide perfusion. Anti-VEGF treatment may reduce these collaterals. In a study, Ferrara et al.[14] were unable to observe collateral vessels forming at the optic nerve head after evaluating the effects of intravitreal bevacizumab (IVB) on six eyes with ME secondary to central retinal vein occlusion (CRVO) with a mean follow-up of 12 months, and they concluded that IVB might have inhibited the formation of collaterals, although VA gain and reduced ME. Similar results were reported by Shah and Shah[15] on a series of nine eyes with CRVO treated with one single injection of 2.5 mg bevacizumab followed by panretinal and grid laser. On the other hand, in their study, Spaide et al.[16] applied e mean number of 8.5 IVR injections for ME secondary to CRVO for 1 year and 55% of the patients developed collateral vessels. In Kokolaki et al.'s[17] study, the patients with ME due to BRVO received a mean number of 7.14±4.75 IVR injections during 26-month mean follow-up and 66.6% of the patients developed collateral vessels. Among the aforementioned studies, 45% of the patients did not develop collateral vessels in the former study, and the number of annual injection was limited in the latter study. In addition, since each intravitreal application could be accompanied by intravitreal hemorrhage or endophthalmitis, we decided to use the protocol as needed.

The ranibizumab for the treatment of ME following branch retinal vein occlusion (BRAVO) study was a 12-month, Phase III, multi-center, randomized trial that included a 6-month, injection-controlled treatment period followed by a 6-month observation period in patients with ME following BRVO. During the treatment period (day 0 to month 5), patients received monthly intraocular injections of

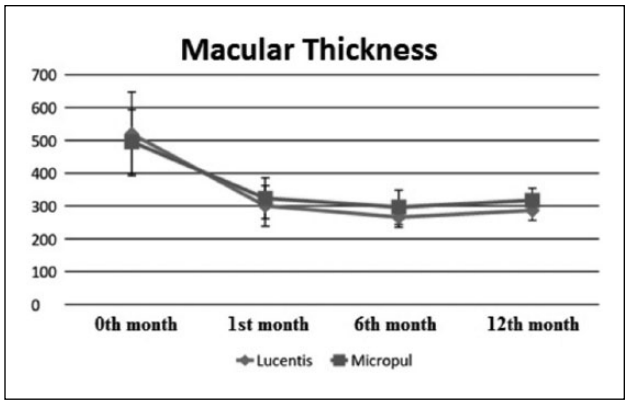

Figure 2. Mean change in central macular thickness from baseline to 12th month.

Table 3. CMT levels at baseline, and at 1st month, 6th month, and 12th month (intra- and inter-group analyses).

CMT	IVR	SML	p[a]
	Mean ± SD	Mean ± SD	
Baseline	519.59 ± 127.36	495.83 ± 97.74	0.463
1st month	300.44 ± 61.93	323.58 ± 61.83	0.189
6th month	265.67 ± 29.93	296.5 ± 52.09	0.011*
12th month	286.37 ± 29.68	317.17 ± 37.42	0.002*
Baseline–1st month p[b]	0.001*	0.001*	
Baseline–6th month p[b]	0.001*	0.001*	
Baseline–12th month p[b]	0.001*	0.001*	

CMT: central macular thickness; IVR: intravitreal ranibizumab; SML: subthreshold micropulse laser.
[a]Student's t test.
[b]Paired sample t test.
*$p < 0.05$.

Table 4. CMT levels at 1st, 6th, 12th month compared to baseline.

CMT	IVR	SML	p[a]
	Mean ± SD	Mean ± SD	
Difference between 1st month and baseline	–219.15 ± 120.3	–172.25 ± 69.84	0.101
Difference between 6th month and baseline	–253.93 ± 132.5	–199.33 ± 77.56	0.076
Difference between 12th month and baseline	–233.22 ± 120.6	–178.67 ± 80.33	0.061

CMT: central macular thickness; IVR: intravitreal ranibizumab; SML: subthreshold micropulse laser.
[a]Student's t test.

0.3 or 0.5 mg ranibizumab or sham injections. During the observation period (months 6–11), all patients received ranibizumab, as needed. At the end of the sixth month, there was an increase of 7.3 letters in the sham group, with 16.6 letters in the 0.3 mg group and 18.3 letters in the 0.5 mg group. In the 0.3 and 0.5 mg treatment groups, these improvements were maintained with as needed ranibizumab during the observation period (6–12 months), with a mean change from baseline BCVA letter score of 16.4 and 18.3, respectively, at 12 months. In the sham group, treatment with ranibizumab as needed for 6 months resulted in rapid reduction in CMT and an improvement in BCVA letter score with a mean change from baseline of 12.1 at 12 months.[18,19] Although the results of early BRAVO studies seemed to be better, there was no difference in long-term outcomes. Also, the results of 12-month follow-up were similar to the IVR patient group in our study. At the end of the first year, a mean of 3.1 injections were done in our IVR group, while 7.8 injections were done in the BRAVO study. The same VA gain can be obtained with application of the protocol PRN from the beginning, as less injections applied, cost and side effects will be reduced. On the other hand, any patients in the sham group were not achieved VA gains from baseline as great as those of patients who received ranibizumab treatment monthly. Greater VA gains might have occurred in the sham group, if patients received as needed therapy from the beginning. Likewise, if our patients had received monthly ranibizumab injections, the increase in VA might be higher than in the micropulse laser group. In a prospective study conducted by Pece et al., 17 patients with ME due to retinal venous occlusion were performed IVR injection. The patients received an injection on day 0 and were, then, retreated as needed. The initial VA in patients with BRVO was 0.80 LogMAR, while it was found to be 0.41 LogMAR at the end of the first year. A mean of 3.6 injections were performed.[20] At the end of the first year, similar results were obtained with our study. These results also showed that although short-term monthly injection provided better VA, there was no difference between long-term results with as needed injection. The fact that the PRN protocols are not regular treatment, and must be assessed on patient basis. As even if no treatment is applied, the prognosis of non ischemic venous occlusions are good.

To the best of our knowledge, studies of micropulse laser for the treatment of ME secondary to RVOs are limited. In the study of Parodi et al.,[21] the effect infrared SML with conventional threshold laser therapy in this entity was compared and no difference between the two groups in terms of VA improvement and resolution of edema was found; however, subthreshold laser was not found to be associated with biomicroscopic and angiographic signs at 2 years. The same researchers recently compared micropulse infrared laser to IVB for the treatment of ME secondary to BRVO recurring after conventional laser therapy and found IVB to be superior in both visual and

anatomical outcomes at 1-year follow-up. Subthreshold laser was administered once, whereas IVB was given at baseline and then on a PRN regimen according to ME presence on OCT.[22] As these patients underwent previous conventional grid laser and consequent development of macular atrophic scars occurred, the number of retinal cells likely to be sensitive to subthreshold laser might be limited. Therefore, the subthreshold laser may have failed, compared to bevacizumab. In addition, Inagaki et al. performed infrared micropulse therapy in patients with BCVA greater than 20/40 in their study and found that VA was maintained for 1 year, CMT decreased significantly at 3rd, 6th, and 12th month. As a result of their study, they showed that micropulse therapy performed in patients with BCVA greater than 20/40 was effective for preserving VA and reducing ME.[23] In all of these studies 810 nm diode laser system with different power settings and duty cycles were used. According to the best of our knowledge, there are no data on the use of yellow micropulse laser in macula edema due to vein occlusion in the literature. Several recent studies have shown that yellow micropulse laser is an effective and safe treatment option for patients with nonresolving CSC and DME.[24–26]

Although the majority of the studies showed efficacy of the SML treatment for CSC, DME, or BRVO, the treatment parameter differed significantly between the individual studies. However, there is no study comparing the outcome of SML with different treatment parameters such as higher and lower duty cycle. Concerning the treatment power, most authors titrated the power individually for each patient. The titration of the power without observing a visible reaction is probably the most challenging part of the SML treatment. As the effect of the treatment was not visible, there is a high risk of undertreatment and treatment failure accordingly. Another risk of this treatment is possibility inadvertent chorioretinal damage due to unintended repetition. Our protocol is safer as it only involves two or three repetitions of very short micropulse laser delivery targeting ME areas, including the fovea. In the present study, no laser scars were detected in any patients after yellow SML treatment. Safety follow-up was performed with OCT, fundus photographies, and FA. The lack of autofluorescence for safety assessment and lack of microperimetry or multifocal electroretinogram for functional evaluation are the limitations of this study. Other limitations are follows: the retrospective design, the lack of a control group, the relatively small sample size, and the lack of long-term assessment of treatment outcomes.

In conclusion, IVR and SML treatment in ME due to BRVO significantly decreases ME and increases the VA. Anti-VEGF therapy is very costly and requires much more follow-up of the patient whereas micropulse therapy is both less costly and requires fewer follow-ups. There is not much work yet with the micropulse laser therapy, which has a very low side effect. Based on our study results, SML therapy may be a suitable alternative to anti-VEGF treatment for ME. Nonetheless, further prospective, randomized, large-scale studies are required to evaluate the therapeutic efficacy and safety of this approach and to identify a more effective treatment protocol employing SML.

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Declaration of conflicting interests

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