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ORIGINAL ARTICLE

Comparative Study Between Subthreshold (Micropulse) Laser Direct Application to the Edematous Macula Versus Direct Application to the Peripheral Healthy Retina in the Treatment of Diabetic Macular Edema

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Abstract

Background: **Subthreshold (micropulse) laser is an effective modality in the treatment of diabetic macular edema that avoids possible complications of conventional laser photocoagulation and anti-vascular endothelial growth factor. Regardless of where the laser is applied, the retinal pigment epithelium is crucial for repair of both outer and inner blood-retinal barriers.**

Aim: **To evaluate both anatomical and functional outcomes of direct application of subthreshold (micropulse) laser to the edematous macula versus to the peripheral healthy retina.**

Patient and methods: **This prospective interventional comparative randomized study was carried out on 30 eyes with diabetic macular edema divided into two groups. Group A included 15 eyes who were treated by direct application of subthreshold micropulse laser to the edematous macula. While group B included 15 eyes who were treated by direct application of subthreshold micropulse laser to the peripheral healthy retina.**

Results: **The study revealed that peripherally treated group (group B) showed rapid improvement of the mean central macular thickness and mean best corrected visual acuity from the first week and first month respectively in contrast with centrally treated group (group A). While both groups showed significant improvement of both mean central macular thickness and mean best corrected visual acuity at 6 months of follow-up.**

Conclusions: **Direct application of subthreshold (micropulse) laser to the peripheral healthy retina is at least as effective as direct application of direct application of subthreshold (micropulse) laser to the centrally affected macula, however, peripherally treated patients showed rapid improvement from the first week of treatment.**

Keywords: Central macular thickness, Diabetic macular edema, Optical coherence tomography, Retinal pigment epithelium, Subthreshold micropulse laser

1. Introduction

Significant vision loss occurs in diabetic patients as a result of diabetic macular edema (DME) with one-third of diabetic patients are affected by DME. The risk of developing DME increases with longer illness duration, the presence of hypertension, and higher hemoglobin A1C (HbA1c).[1]

Laser photocoagulation had been the main option in the treatment of DME, but its destructive nature causes permanent damage to the retinal cells, resulting in adverse effects such as central visual loss, field defects, and decreased night vision.[2,3]

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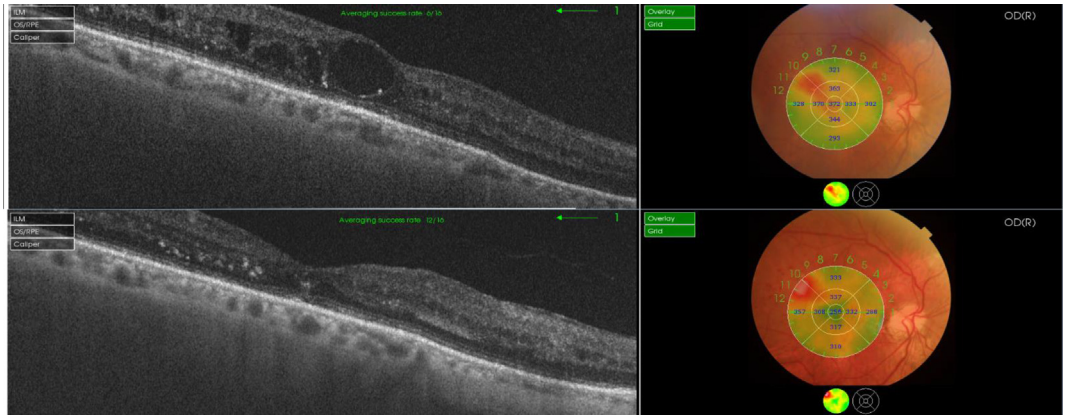

Fig. 1. 64 years old male patient with cystoid macular edema. CMT improved within 6 weeks from 372 μm to 256 μm after direct application of SML to the peripheral healthy retina.

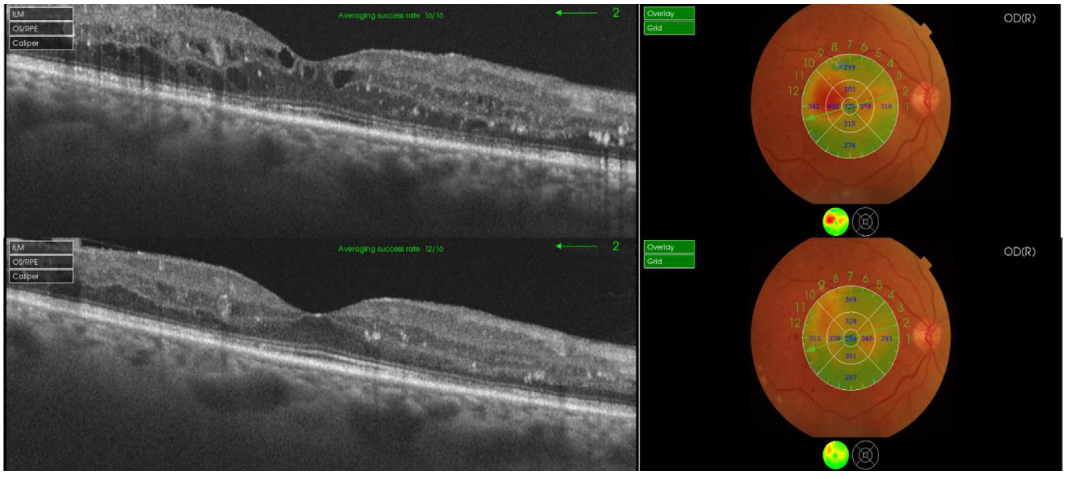

Fig. 2. 55 years old female patient with cystoid macular edema. CMT improved within 7 weeks from 320 μm to 269 μm after direct application of SML to the peripheral healthy retina.

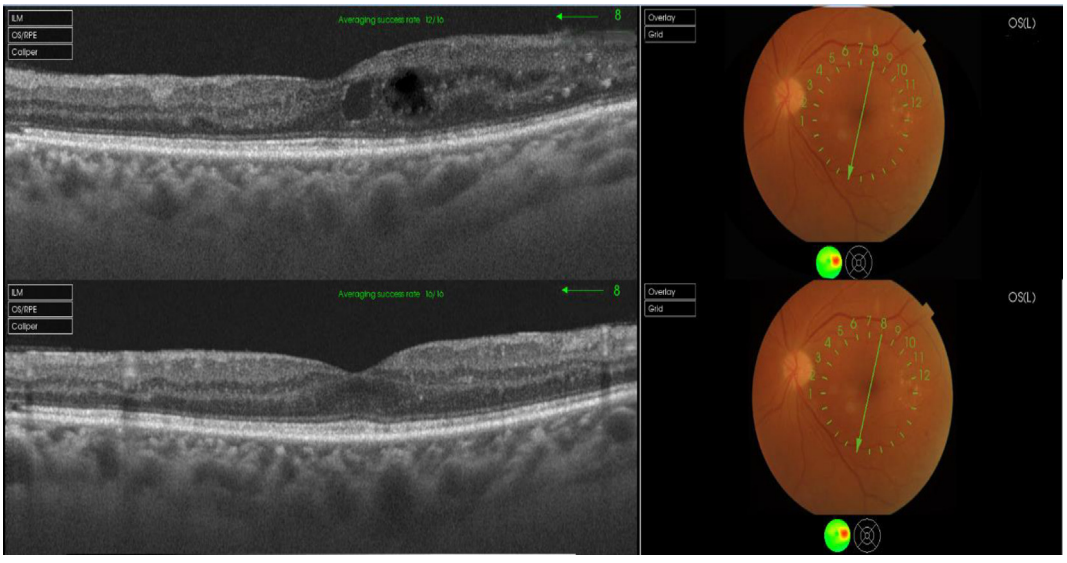

Fig. 3. 59 years old female patient with cystoid macular edema. CMT improved within 2 months from 354 μm to 257 μm after direct application of SML to the peripheral healthy retina.

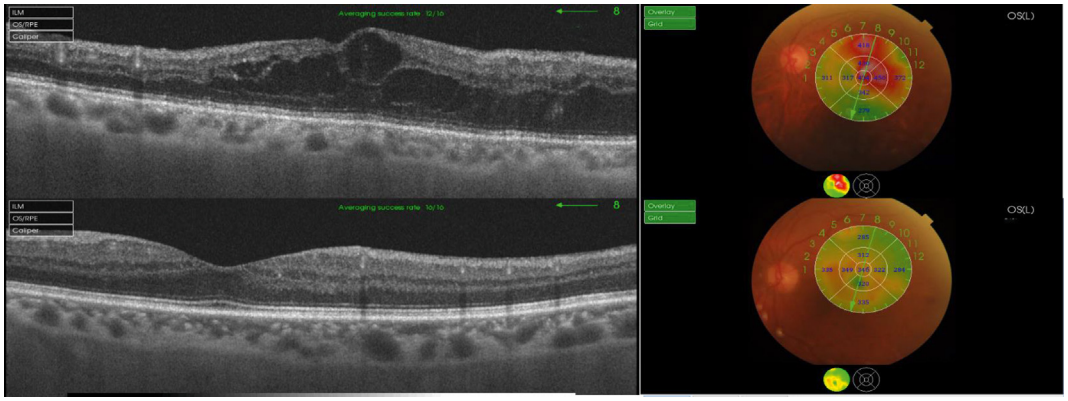

Fig. 4. 52 years old female patient with cystoid macular edema. CMT improved within 3 months from 434 μm to 346 μm after direct application of SML to the peripheral healthy retina.

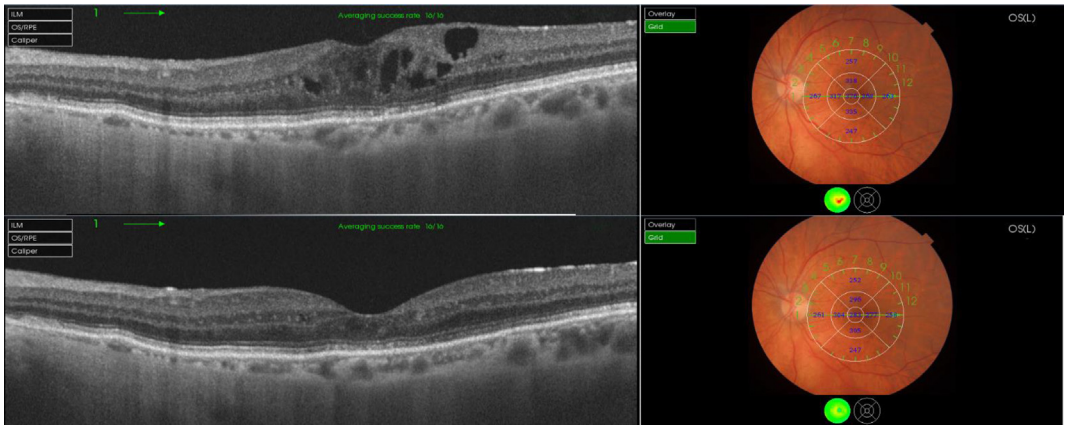

Fig. 5. 55 years old female patient with cystoid macular edema. CMT improved within 4 months from 376 μm to 283 μm after direct application of SML to the peripheral healthy retina.

Subthreshold (micropulse) laser (SML) is a treatment modality which is effective as traditional laser treatment; however, SML is safer as there is no damage produced to retinal pigment epithelium (RPE). Safety of SML is clinically demonstrated by no burn observations throughout treatment and by the absence of laser effect on fundus fluorescein angiography (FFA).[4]

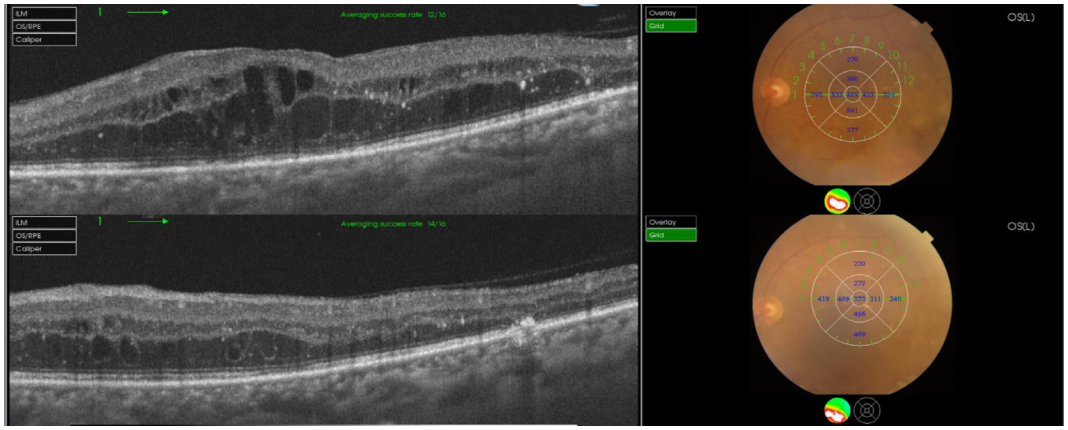

Fig. 6. 60 years old female patient with cystoid macular edema and intraretinal edema. CMT improved within 6 months from 489 μm to 373 μm after direct application of SML to the peripheral healthy retina.

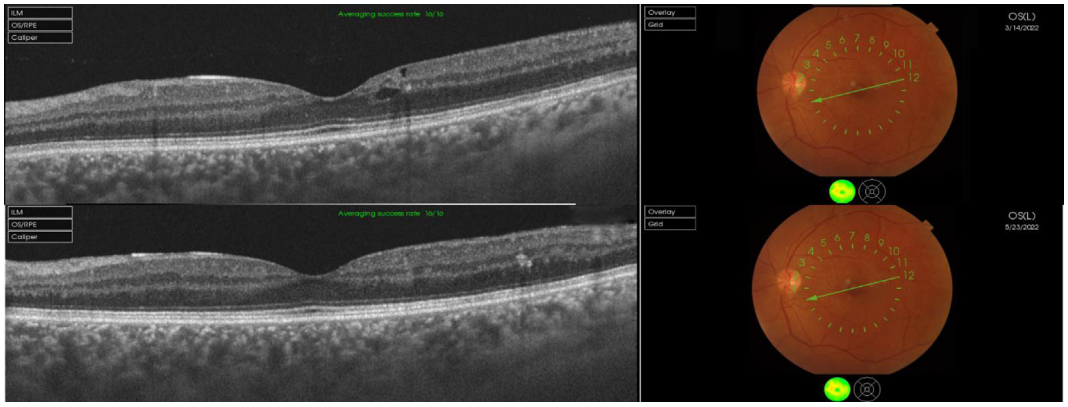

Fig. 7. 60 years old female patient with cystoid macular edema. CMT improved within 11 weeks from 335 μm to 281 μm after direct application of SML to the central retina at the macula.

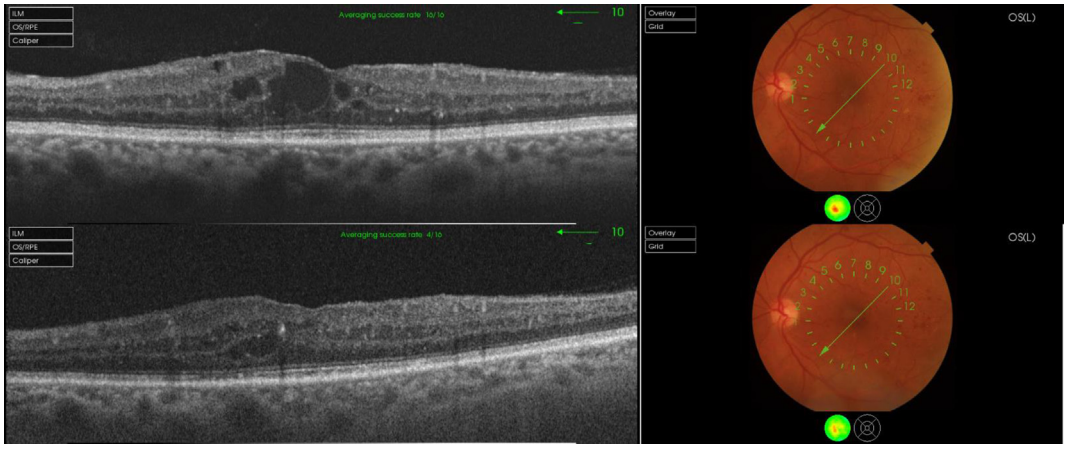

Fig. 8. 57 years old female patient with cystoid macular edema. CMT improved within 6 months from 386 μm to 325 μm after direct application of SML to the central retina at the macula.

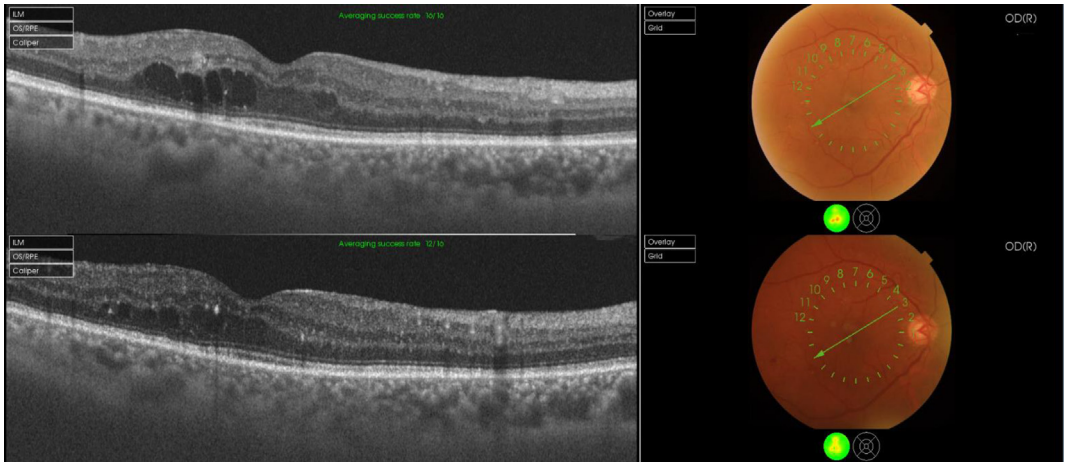

Fig. 9. 62 years old female patient with cystoid macular edema. CMT improved within 6 months from 349 μm to 301 μm after direct application of SML to the central retina at the macula.

The laser energy emitted activates cells without causing structural damage. This results in the beneficial alteration of retinal inflammatory process, with the blood-retinal barrier being restored as a result. Additionally, recent research in humans has shown that SML reduces a number of local factors (growth factors, growth inhibitors and permeability factors, etc.) which accelerate the harmful diabetic process.[5–7]

This study aims to evaluate both anatomical and functional outcomes of direct application of SML to the edematous macula versus to the peripheral healthy retina.

2. Patient and methods

The study is a prospective interventional comparative randomized study which was carried out on 30 eyes of 24 patients with DME attending outpatient clinic at Sayed Galal university hospital of Al-Azhar university. The study was approved by the local ethical committee of Al-Azhar University. Each patient gave their informed consent after being informed of the study's purpose, methods, potential dangers, and advantages.

The study included 30 eyes of 24 patients with DME (7 males and 17 females). The included patients had DME detected by the presence of intraretinal or subretinal fluid involving the fovea using optical coherence tomography (OCT). Inclusion criteria are patients who had central foveal thickness less than 500 μm and both type one and type two diabetic patient. Exclusion criteria are patients who had undergone intraocular surgery, laser treatment, or intravitreal injection (IVI) at least six months previously to the trial, as well as those with central macular thickness (CMT) > 500 μm on OCT.

The treated eyes were divided into two groups at random. Group A (centrally treated group) that were treated by direct application of SML to the edematous macula. While group B (peripherally treated group) that were treated by direct application of SML to the peripheral healthy retina. All patients underwent history taking that included age, sex, DM duration, prior glycemic management (HbA1c), medications, IVI, laser photocoagulation, and ocular surgery. Full ophthalmic examination by slit lamp to assess media clarity and posterior segment examination using slit lamp with +90 volk lens.

Each appointment included measuring the patient's uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA) using the Snellen chart with converting the results to decimal acuity for statistical analysis. Automated refraction by (Topcon Auto-refractometer RM 8900). The Topcon DRI OCT Triton plus was used to conduct the OCT examination. Prior to treatment, CMT was assessed, and then once a week for the first month and then once a month for the following six months.

IRIDEX IQTM 532 nm lasers were used during laser therapy sessions (Mountain View, CA, USA) with macula lens (1.05 magnification) were used to visualize the fundus. At each session all eyes received prelaser pupillary dilation with tropicamide 0.5%. Topical anesthesia with 1–2 drops of 0.4% benoxinate was administered 3–5 min before each laser session.

In each case, the same fixed treatment follows: 200 ms exposure duration, 300 μm spot size, 400 mW power, and a 5% duty cycle while number of shots were adjusted according to severity of DME as the more sever the edema the higher the shots number and follow-up were scheduled weekly for a month then monthly for six months. If the edema continued or got worse in comparison to the baseline OCT, retreatment was done. If improvement was found no laser was performed. The follow-up evaluation included BCVA measurement and OCT imaging (Figs. 1–9).

3. Results

Between February and October 2022, 30 eyes of 24 patients were engaged in the study. Total of 24/24 patients completed follow-up until 6 months.

Group A (centrally treated group) consisted of 15 eyes from 12 patients 8 female patients and 4 male patients (7 right, 8 left and 9 unilateral, 3 bilateral). The patients had a mean age of 58.33 ± 6.93 years, with a mean duration of DM of 10.08 ± 4.89 years and mean HbA1c was 8.20 ± 0.62% and 7.77 ± 0.62% at baseline and 6 months respectively. Group B (peripherally treated group) contained 15 eyes from 12 patients (6 right, 9 left and 9 unilateral, 3 bilateral). The patients had a mean age of 57.00 ± 10.59 years, with mean duration of DM of 8.58 ± 4.44 years and mean HbA1c was 8.08 ± 0.80% and 7.71 ± 0.80% at baseline and 6 months respectively. As regard group A there were 4 eyes received previous intravitreal injections more than 6 months prior to the study and no eyes received laser treatment. However, for the group B there were 3 eyes received previous intravitreal injections and one eye received laser treatment more than 6 months from prior to the study. No patient in both groups underwent previous ocular surgery. No statistically significant difference between two groups regarding patient's sex, age, diabetes duration or HbA1c, previous IVI or Previous retinal laser. Table 1.

Table 1. NO significant difference between 2 groups regarding the mean age, sex, eye side, laterality of the eye, IVI, diabetes duration, HbA1c at baseline or HbA1c at the end of the study.

	Group A	Group B	Test value	*P* value	Sig.
Age of patient					
Mean ± SD	58.33 ± 6.93	57.00 ± 10.59	0.365•	0.719	NS
Range	42–71	30–70			
Sex of patient					
Male	4 (33.3%)	3 (25.0%)	0.202*	0.653	NS
Female	8 (66.7%)	9 (75.0%)			
Eye side					
Right	7 (46.7%)	6 (40.0%)	0.136*	0.713	NS
Left	8 (53.3%)	9 (60.0%)			
Laterality of the eye					
Unilateral	9 (75.0%)	9 (75.0%)	0.000*	1.000	NS
Bilateral	3 (25.0%)	3 (25.0%)			
Intravitreal injections					
Previous IVI	4 (26.7%)	3 (20.0%)	0.186*	0.666	NS
No previous IVI	11 (73.3%)	12 (80.0%)			
Duration of diabetes					
Mean ± SD	10.08 ± 4.89	8.58 ± 4.44	0.787•	0.440	NS
Range	4–20	2–19			
HbA1c baseline					
Mean ± SD	8.20 ± 0.62	8.08 ± 0.80	0.400•	0.693	NS
Range	7.3–9.1	7–9.5			
HbA1c 6 months					
Mean ± SD	7.77 ± 0.62	7.71 ± 0.80	0.200•	0.843	NS
Range	6.7–8.7	6.5–9.3			
Laser photocoagulation					
Previous LPC	0 (0.0%)	1 (6.7%)	1.034*	0.309	NS
No previous LPC	15 (100.0%)	14 (93.3%)			

P value > 0.05: Non significant; *P* value < 0.05: Significant; *P* value < 0.01: Highly significant.
*: Chi-square test.
•: Independent *t*-test.

In group A, mean BCVA were stable at 1 month (0.18 ± 0.12) (*P* value > 0.05) while improved at 6 months of follow-up to (0.23 ± 0.15) (*P* value < 0.05) as compared by baseline (0.18 ± 0.12). Table 2.

On the other hand, in group B, mean BCVA showed significant improvement after 1 month (0.25 ± 0.11) (*P* value < 0.05) and highly significant improvement at 6 months (0.30 ± 0.12) (*P* value < 0.01) of follow-up compared to baseline (0.21 ± 0.11). Table 3.

As regard OCT, in Group A, mean CMT was stable at 1 week (374.49 ± 42.94 μm) and one month (355.6 ± 54.87 μm) (*P* value > 0.05) compared with baseline (375.93 ± 45.61 μm) and showed highly significant improvement to (297.47 ± 41.57) (*P* value < 0.01) after 6 months of follow-up. Table 4.

On the other hand, in Group B, mean CMT showed highly significant improvement from (381.27 ± 47.08 μm) at baseline to (374.39 ± 47.04 μm) and (336.79 ± 38.97 μm) at one week and one month respectively and to (278.46 ± 36.00 μm) (*P* value < 0.01) after 6 months of follow-up. Table 5.

As regard CMT changes along the follow-up period of group A, 11 eyes were stable, 3 eyes get worse and 1 eye improved after 1 week of the first SML session. After 1 month 8 eyes were stable, 1 eye

Table 2. Mean BCVA of group A over 6 months follow-up showed stabilization over 1 month and significant improvement over 6 months.

BCVA	Group A			Test value	*P* value	Sig.
	Baseline	1 month	6 months			
Mean ± SD	0.18 ± 0.12	0.18 ± 0.12	0.23 ± 0.15			
Range	0.05–0.4	0.05–0.4	0.05–0.5	10.850≠	0.004	HS
Difference	–	0.001 ± 0.045	0.053 ± 0.074			
Post hoc analysis						
Baseline versus 1 month			**Baseline versus 6 months**		**1 m versus 6 m**	
0.854			0.032		0.020	

P value > 0.05: Non significant; *P* value < 0.05: Significant; *P* value < 0.01: Highly significant.
≠: Friedman test.

Table 3. Mean BCVA of group B over 6 months follow-up showed significant improvement from the first month of treatment.

BCVA	Group B			Test value	*P* value	Sig.
	Baseline	1 month	6 months			
Mean ± SD	0.21 ± 0.11	0.25 ± 0.11	0.30 ± 0.12			
Range	0.05–0.4	0.05–0.4	0.05–0.5	15.511≠	<0.001	HS
Difference		0.041 ± 0.066	0.095 ± 0.081			
Post hoc analysis						
Baseline versus 1 month			**Baseline versus 6 months**		**1 m versus 6 m**	
0.042			0.003		0.023	

P value > 0.05: Non significant; *P* value < 0.05: Significant; *P* value < 0.01: Highly significant.
≠: Friedman test.

get worse and 6 eyes were improved. However, at 6 months follow-up 5 eyes were stable, 1 eye get worse and 9 eyes were improved.

As regard CMT changes along the follow-up period in group B, 10 eyes were stable, 1 eye get worse and 4 eyes improved after 1 week of the first SML session. After 1 month 4 eyes were stable, no eyes get worse and 11 eyes improved. However, at 6 months follow-up 2 eyes were stable, 1 eye get worse and 12 eyes showed improvement.

There was no statistically significant difference between both groups regarding the improvement of mean CMT and mean BCVA by the end of follow-up period. Tables 6 and 7.

The mean number of shots per session was 579.60 ± 73.40 shots while the mean number of sessions was 7.47 ± 1.69 for group A. While the mean number of shots per session for group B was 568.20 ± 88.57 and the mean number of sessions was 6.33 ± 1.45 session with no statistically significant difference between both groups. Table 8.

4. Discussion

Hypotheses were created to clarify the mechanism of conventional laser originated from the presumption that retinal damage produced during treatment was vital to deliver the useful therapeutic impact.[8–10] While laboratory studies showed that the therapeutic effect elicited by conventional laser in the form of modulation in retinal pigment epithelium (RPE) cytokine production come from cells which are stimulated and not killed by laser burn at the margins of conventional laser burns. Therefore, the damage produced by conventional laser isn't necessary to produce the therapeutic effect.[11,12]

SML is a tissue-sparing laser technique that avoids the limitations of photocoagulation.[5] In addition to the absence of retinal damage, SML does not produce inflammation or destruct the viable healthy retina.[13]

The RPE is crucial for restoring the inner and outer inner blood-retinal barriers independent of the type and location of laser treatment. The absence of chorioretinal laser damage permits retreatment of the same location and allows for the overlapping application of laser shots without concern of producing retinal scarring.[14] So, in this study we applied laser to the peripheral healthy retina and to the central edematous retina in repetitive manner without fear of retinal damage to achieve the desirable effect.

The first study of micropulse laser demonstrated reduction in diabetic macular edema in more than 87% of the patients.[9] Laursen et al. demonstrated similar results when comparing standard SML to a conventional argon laser.[15]

Table 4. Mean CMT of group A showed stabilization over the first month of treatment while highly significant improvement occurred at 6 months of follow-up.

CMT	Group A				Test value	*P* value	Sig.
	Baseline	1 week	1 month	6 months			
Mean ± SD	375.93 ± 45.61	374.49 ± 42.94	355.60 ± 54.87	297.47 ± 41.57			
Range	301–451	295–447.7	271–490	251–391	15.066•	<0.001	HS
Difference	–	−1.44 ± 7.90	−20.33 ± 46.78	−78.47 ± 62.59			
Post hoc analysis							
Baseline			**1 week**		**1 month**		
1 week	**1 month**	**6 months**	**1 month**	**6 months**	**6 months**		
1.000	0.687	0.002	0.845	0.001	0.025		

P value > 0.05: Non significant; *P* value < 0.05: Significant; *P* value < 0.01: Highly significant.
•: Repeated Measures ANOVA test.

Table 5. Mean CMT of group B showed highly significant improvement from the first week of treatment.

CMT	Group B				Test value	*P* value	Sig.
	Baseline	1 week	1 month	6 months			
Mean ± SD	381.27 ± 47.08	374.39 ± 47.04	336.79 ± 38.97	278.46 ± 36.00			
Range	289–491	285.6–488.4	254–420.9	241–351	28.084•	<0.001	HS
Difference		−6.88 ± 6.59	−44.48 ± 38.36	−102.81 ± 64.97			
Post hoc analysis							
Baseline			**1 week**		**1 month**		
1 week	**1 month**	**6 months**	**1 month**	**6 months**	**6 months**		
0.007	0.003	<0.001	0.019	<0.001	0.005		

P value > 0.05: Non significant; *P* value < 0.05: Significant; *P* value < 0.01: Highly significant.
•: Repeated Measures ANOVA test.

Table 6. No statistically significant difference between both group regarding mean CMT after 6 months of follow-up.

CMT	Group A	Group B	Test value	*P* value	Sig.
Difference after 6 months central					
Mean ± SD	−78.47 ± 62.59	−102.81 ± 64.97	−1.099≠	0.272	NS
Range	−197–17	−240 to −9			

P value > 0.05: Non significant; *P* value < 0.05: Significant; *P* value < 0.01: Highly significant.
≠: Mann–Whitney test.

It is well-established that SML is as effective as traditional laser in improving BCVA and CMT.[16–18] The improvement of CMT is maintained during follow-up. Additionally, the visual acuity was enhanced while maintaining contrast sensitivity without any loss of visual field or scotomas.[16,17] Microperimetry showed enhancement of retinal sensitivity with SML compared to traditional laser.[16] Moreover, repeated transscleral micropulse diode laser to peripheral healthy retina which is called (Taha Technique) was found to be an easy-to-use, effective, and safe treatment technique for stimulation of peripheral healthy RPE.[19]

It is noted that group B showed highly significant improvement of mean CMT from the first week of treatment in contrast to group A which showed stabilization of mean CMT at the first week and first month which suggests that stimulation of healthy RPE at the peripheral healthy retinal was more effective than stimulation of the diseased RPE at central edematous macula. Tables 4 and 5.

Table 7. No statistically significant difference between both group regarding mean BCVA after 6 months of follow-up.

BCVA	Group A	Group B	Test value	*P* value	Sig.
Difference after 6 months					
Mean ± SD	0.053 ± 0.074	0.095 ± 0.081	−1.771≠	0.076	NS
Range	−0.11–0.2	−0.1–0.25			

P value > 0.05: Non significant; *P* value < 0.05: Significant; *P* value < 0.01: Highly significant.
≠: Mann–Whitney test.

Table 8. No statistically significant difference between both group regarding number of sessions or number of shots per session.

	Group A	Group B	Test value	*P* value	Sig.
Shots per session					
Mean ± SD	579.60 ± 73.40	568.20 ± 88.57	0.384•	0.704	NS
Range	441–690	402–743			
Number of sessions					
Mean ± SD	7.47 ± 1.69	6.33 ± 1.45	1.976•	0.058	NS
Range	5–12	4–9			

P value > 0.05: Non significant; *P* value < 0.05: Significant; *P* value < 0.01: Highly significant.
•: Independent *t*-test.

Functionally, mean BVCA of group B showed significant improvement at 1 month in contrast to group A which showed stabilization of mean BCVA at 1 month of follow-up which also suggests the superiority of the healthy RPE stimulation over the diseased RPE. Tables 2 and 3.

While there was no statistically significant difference between both groups concerning CMT and BCVA at 6 of follow-up, it is noted that group B showed rapid improvement from the first week of treatment. Tables 5–7.

4.1. Conclusions

Direct application of subthreshold (micropulse) laser to the peripheral healthy retinal is at least as effective as direct application of the subthreshold (micropulse) laser to the centrally affected macula, however, results of peripherally treated patients showed rapid improvement from the first week of treatment. Additionally, regarding the statistical non significant difference between 2 groups at 6 months of follow-up, long term period of follow-up and larger number of patients may be required.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article.

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Conflicts of Interest

There are no conflicts of interest.

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