SUBTHRESHOLD MICROPULSE DIODE LASER VERSUS CONVENTIONAL LASER PHOTOCOAGULATION FOR DIABETIC MACULAR EDEMA

A Meta-Analysis of Randomized Controlled Trials

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Purpose: To evaluate the relative efficacy of subthreshold micropulse diode laser versus conventional laser photocoagulation for the treatment of diabetic macular edema.

Methods: A comprehensive literature search was conducted to find relevant randomized controlled trials (RCTs). Efficacy estimates were determined by comparing weighted mean differences of the mean change of best-corrected visual acuity and central macular thickness from baseline.

Results: Six RCTs were selected for this meta-analysis, including 398 eyes (203 eyes in the subthreshold micropulse diode laser group and 195 eyes in the conventional laser group). Subthreshold micropulse diode laser was superior to conventional laser in terms of mean change of logMAR best-corrected visual acuity at 3, 9, and 12 months after treatment ($P = 0.02$; $P = 0.04$, and $P = 0.03$, respectively), and it showed a similar trend at 6 months ($P = 0.05$). Although, there was no significant difference in terms of mean change in central macular thickness from baseline to 3, 6, 9, or 12 months ($P = 0.80$; $P = 0.20$; $P = 0.88$, and $P = 0.86$, respectively).

Conclusion: Subthreshold micropulse diode laser treatment resulted in better visual acuity compared with conventional laser, although the differences before 12 months are likely to be too small to be of clinical relevance and may be dependent on baseline best-corrected visual acuity. The two types of treatment seem to have similar anatomical outcome.

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Diabetic retinopathy is the most frequent and severe ocular complication of diabetes mellitus, the leading cause of blindness in the working-age population in developed countries.[1] Diabetic macular edema (DME) is a major contributor to vision loss and one of the main causes for decreased visual acuity in patients with diabetic retinopathy.[2] The prevalence of DME increases from 0% to 3% in individuals recently diagnosed with diabetes to 28% to 29% in those with a diabetes duration of more than 20 years.[3]

The conventional laser (CL) photocoagulation, applied either as a focal or grid pattern and typically using an argon laser (514 nm) or double-frequency Nd-YAG laser (532 nm) was shown by the Early Treatment Diabetic Retinopathy Study to reduce the risk of significant vision loss by 50% and has been the standard of care for DME since the mid-80s.[4] Moreover, focal/grid laser treatment was shown to be more effective and to have fewer side effects compared with two doses of intravitreal triamcinolone in a multicenter

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randomized clinical trial by the Diabetic Retinopathy Clinical Research Network at both 2- and 3-year follow-ups.[5,6] However, the beneficial effect of CL is associated with destruction of retinal photoreceptors, progressive enlargement of laser retinal scars (in some cases leading to a foveal atrophy), and development of choroidal neovascularization and subfoveal fibrosis.[7–10] Moreover, despite the proven benefit in stabilization of central visual acuity, laser photocoagulation for DME invariably results in a localized loss of perimetric sensitivity within 10° eccentricity of the fovea.[7,11] These complications have been attributed to spread of thermal energy from individual laser burns and collateral damage to adjacent neural retina and choroidal layers with continuous-wave laser therapy.

To reduce this collateral damage, other wavelengths in the infrared part of the spectrum (810 nm), typically delivered by a diode laser, have been introduced in the management of DME. This was supplemented by a different modality for delivery of the laser light such as micropulse laser delivery.[12] In this modality, the laser energy is delivered in short pulses ("micropulses"), typically within a 100- to 300-milliseconds "on" cycle and 1700- to 1900-milliseconds "off" cycle rather than as a continuous wave with hundreds of milliseconds cycle duration as with the CL. The longer "off" interval allows for heat dissipation and confines the energy transfer to the tissue with maximal absorption of laser energy, in this case—the melanocytes within the retinal pigment epithelium. This treatment was named subthreshold micropulse diode laser (SDM) treatment because there is no visible scarring and the individual burns remain below the threshold of observability. Histological studies have indicated that when applying 810-nm laser pulses of microsecond duration, the laser energy affects almost exclusively the retinal pigment epithelium, with very little damage to the overlying neural retina or the underlying choriocapillaris.[13] Therefore, the abovementioned heat-induced complications associated with the conventional continuous-wave laser treatment may be decreased by this type of treatment, which can lead to less negative effects on visual function. However, it may be possible that the smaller amount of laser energy per treatment may not be as effective as in CL mode to reduce macular edema and therefore to decrease central macular thickness (CMT). To the best of our knowledge, there has been no meta-analysis of randomized controlled trials (RCTs) comparing the outcomes of SDM versus CL in patients with DME. Therefore, we undertook a meta-analysis of all available RCTs to assess the efficacy of these two treatments for the management of DME.

Methods

This meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement.[14]

Search Strategy

We conducted searches of PubMed, ClinicalTrials.gov, and the Cochrane Library using the terms *diabetic macular edema or DM and subthreshold micropulse diode laser or SDM*. A manual search was performed by checking the reference lists of original reports and review articles to identify studies not yet included in the computerized databases. The final search was performed on October 1, 2015, without restrictions regarding publication year or language.

Inclusion and Exclusion Criteria

Articles were considered eligible for inclusion in the meta-analysis if the studies met the following inclusion criteria: 1) study design: RCT, 2) population: DME without previous treatment, 3) intervention: SDM versus CL, and 4) outcome variables: at least one of the outcomes of interest discussed in the section Outcome Measures below. Abstracts from conferences, full texts without raw data available for retrieval, duplicate publications, letters, and review articles were excluded. When sequential reports on the same cohort of patients were considered, only the most recent report was included, and data that could not be obtained from this last publication were obtained from the previous reports.

Outcome Measures

The primary outcome measure was the mean change in logarithm of the minimal angle of resolution (logMAR) best-corrected visual acuity (BCVA) from baseline. The secondary outcome measure was the mean change in CMT from baseline.

Data Extraction

The data were extracted independently by two reviewers (G.C. and W.L.). Disagreement was resolved by discussion. The information extracted from each study included the authors of each study, the year study was reported, information on the study design, location of the trial, duration of the study, number of subjects, the mean change in BCVA presented as logMAR, and the mean change in CMT measured with optical coherence tomography and presented as change in micrometers of total retinal thickness.

Qualitative Assessment

The qualities of RCTs were assessed by two independent observers (F.J. and S.M.) using a Jadad scale,[15] allocating 1 point for the presence of each of the following: randomization, masking, and participant withdrawals/dropouts. If randomization and blinding were appropriate, 1 additional point was added for each. Thus, the total score ranged from 0 to 5. Studies scoring less than three points were considered to be of low quality.

Statistical Analysis

The quantitative data were entered into the Cochrane Review Manager (RevMan; software version 5.1; Copenhagen, Denmark: The Nordic Cochrane Center, The Cochrane Collaboration, 2011). For continuous variables (e.g., BCVA), the weighted mean difference (WMD) was measured, outcome was reported with a 95% CI. $P < 0.05$ was considered statistically significant on the test for overall effect. The I^2 statistic was calculated to assess heterogeneity between studies ($P < 0.05$ was considered representative of significant statistical heterogeneity).[16] If there was heterogeneity between studies, a random-effects model was applied to the data. Alternatively, a fixed-effects model was used for pooling the data. For continuous variables, percent weights were based on SD: smaller SD resulted in greater percent weight.[17] Begg's rank correlation test and Egger's linear regression test were used to quantitatively assess publication bias ($P < 0.05$ was considered representative of significant statistical publication bias).[18,19]

Results

Overall Characteristics of Selected Trials and Quality Assessment

A total of 48 articles were initially identified. Of these, 42 were rejected according to the exclusion criteria listed above. Hence, a total of six studies were included in this meta-analysis.[20–25] A flow diagram of the search procedure and results is provided in Figure 1. One study (Lavinsky et al[22]) had three treatment groups (CL, normal-density SDM, and high-density SDM). Based on the reported effects on the visual acuity and interpretation of other authors,[26] the high-density treatment group was selected for this meta-analysis. In total, there were 398 eyes included in this meta-analysis. Of note, 203 eyes were included in the SDM group, and 195 eyes were included in the CL group. All studies fulfilled the quality criteria (three points or more). In all the included studies, no statistical significant differences in the visual acuity were reported between the SDM group and CL group at baseline. The characteristics of the studies included and quality scores are summarized in Table 1.

Effects on Best-Corrected Visual Acuity

Four studies involving 215 eyes compared SDM with CL in terms of mean change in logMAR BCVA at 3 months and 6 months from baseline and two studies involving 146 eyes reported results at 9 and 12 months. Overall, all results demonstrated good stabilization of visual acuity with both types of treatment. Nevertheless, SDM seemed to be superior to CL in terms of mean change in logMAR BCVA at 3, 9, and 12 months after treatment (WMD = −0.06, 95% CI: −0.12 to −0.01, $P = 0.02$; WMD = −0.09, 95% CI: −0.17 to 0.00, $P = 0.04$; and WMD = −0.10, 95% CI: −0.19 to −0.01, $P = 0.03$, respectively), whereas it showed the same trend but no statistical significance at 6 months (WMD = −0.06, 95% CI: −0.12 to 0.00, $P = 0.05$), with no heterogeneity identified (Figure 2).

Effects on Central Macular Thickness

Four studies involving 215 eyes compared SDM with CL in terms of mean change in CMT at 3 months after treatment, five studies (314 eyes) reported results at 6 months, two studies (146 eyes) at 9 months, and three studies (230 eyes) at 12 months. As with visual acuity, overall, the results showed that both treatments were efficacious in reducing CMT at all follow-up time points. There were no significant difference between SDM and CL in the mean change of CMT at any time after treatment (WMD = −2.52, 95% CI: −21.57 to 16.52, $P = 0.80$; WMD = −7.68, 95% CI: −19.34 to 3.98, $P = 0.20$; WMD = −2.60, 95% CI: −37.55 to 32.36, $P = 0.88$; and WMD = −2.49, 95% CI: −30.44 to 25.46, $P = 0.86$, respectively), with no heterogeneity identified (Figure 3). Begg's rank correlation test and Egger's linear regression test indicated no publication bias for any of the parameters.

Discussion

In this meta-analysis, we reviewed the results from six RCTs, including a total of 398 eyes (203 eyes in the SDM group and 195 eyes in the CL group). In terms of the effect on central visual acuity, both treatment modalities demonstrated good stabilization effect up to 12 months after treatment. Still, although

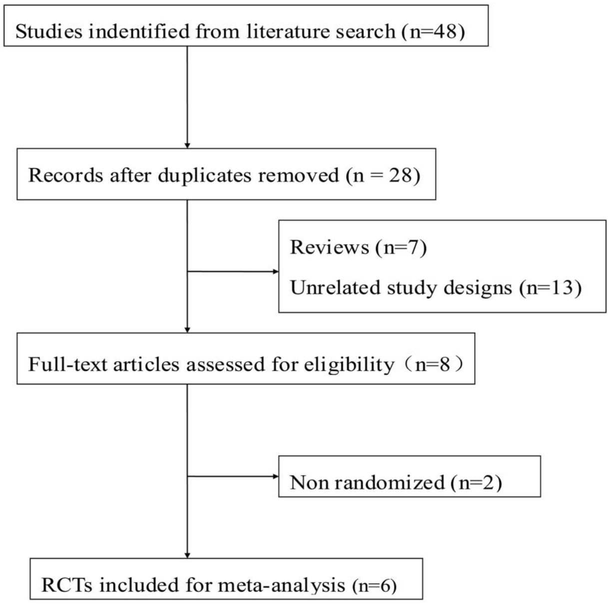

Fig. 1. Flow diagram of studies included in this meta-analysis. RCT, randomized controlled trial.

none of the studies demonstrated any statistical difference between the two treatments, when aggregated within this meta-analysis, the results from applying SDM treatment seemed to be superior in stabilizing BCVA compared with CL treatment at all time points up to 12 months. Both treatments substantially reduced fluid in or under the retina, and SDM demonstrated equivalent efficacy when compared with CL at all follow-up time points.

Subthreshold micropulse diode laser treatment is based on the principle of applying low energy per single pulse, in an attempt to confine the place of interaction of laser energy with the retina to the retinal pigment epithelium cells and avoid thermal spread to the surrounding tissue.[13] Figueira et al[20] found that less laser scars were detected in the SDM group compared with the CL group. This is an important finding, as spread of retinal atrophy around laser scars produced by a continuous-wave laser occurs over the years and is a frequent complication, particularly for macular laser.[27] Vujosevic et al[24] found that central retinal sensitivity determined by microperimetry was improved after treatment in the SDM group at 12 months, whereas it decreased in the CL group at the same time point. Similarly, Venkatesh et al[23] found that central visual function was better maintained after SDM treatment compared with the results after CL treatment based on multifocal electroretinograpy, likely a result of lesser collateral thermal damage to the neural retina. In the current meta-analysis unexpected adverse effects of both treatment modalities were minimal and theoretically, the less destructive nature of the micropulse approach could explain the better visual acuity outcome despite the comparable decrease in total retinal thickness observed with both treatments at the same time points.

Current treatment options for DME allow for varied and increasingly complex combinations of treatment paradigms such as laser monotherapy, combination of laser therapy with anti–vascular endothelial growth factor (anti-VEGF) agents (RBZ, bevacizumab, and aflibercept), anti-VEGF monotherapy, and sustained-release corticosteroid therapy (dexamethasone, either as a monotherapy or in combination with the other

Table 1. Characteristics and Quality Scores of Included Studies

Study Group, Year	Design	Location	Follow-up, Months	Laser Wavelength, nm	No. Eyes	Age, Year	Baseline BCVA (SD)	Approximate Snellen Acuity*	Jadad Score
Figueira, 2009	RCT	Portugal and United Kingdom	12	810	44	59.8	78.4 (8.1)†	~20/50 −2	5
				514	40	61.1	78.0 (7.8)†	~20/50 −2	
Laursen, 2004	RCT	Denmark	6	810	12	61	0.70 (0.36)‡	~20/100	3
				514	11	61	0.62 (0.17)‡	~20/80 −1	
Lavinsky, 2011	RCT	Brazil	12	810	42	61.9	0.90§	~20/160	5
				532	42	61.8	0.80§	~20/125	
Venkatesh, 2011	RCT	India	6	810	23	NA	0.41 (0.30)‡	~20/50	3
				532	23	NA	0.33 (0.20)‡	~20/40 −1	
Vujosevic, 2010	RCT	Italy	12	810	32	62.8	0.21 (0.30)‡	~20/32	3
				514	30	62.1	0.29 (0.30)‡	~20/40	
Xie, 2013	RCT	China	6	810	50	58	0.23 (0.18)‡	~20/32 −1	3
				514	49	56	0.21 (0.18)‡	~20/32	

*Approximate conversion to Snellen visual acuity values is based on Table RR-2 (http://dicom.nema.org/DICOM/2013/output/chtml/part17/sect_RR.2.html).
†Mean BCVA in ETDRS letter scores.
‡Mean BCVA in logMAR.
§Median BCVA in logMAR.
NA, not available.

Study or Subgroup	SDM Mean	SDM SD	SDM Total	CL Mean	CL SD	CL Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 Mean change in logMAR best-corrected visual acuity from baseline (3 months)								
Laursen 2004	-0.01	0.19	12	0.06	0.2	11	11.6%	-0.07 [-0.23, 0.09]
Lavinsky 2011	-0.12	0.18	42	-0.04	0.14	42	62.3%	-0.08 [-0.15, -0.01]
Venkatesh 2011	0	0.3	23	0.03	0.2	23	13.7%	-0.03 [-0.18, 0.12]
Vujosevic 2010	0.01	0.3	32	0.03	0.32	30	12.4%	-0.02 [-0.17, 0.13]
Subtotal (95% CI)			**109**			**106**	**100.0%**	**-0.06 [-0.12, -0.01]**
Heterogeneity: Chi² = 0.73, df = 3 (P = 0.87); I² = 0%								
Test for overall effect: Z = 2.32 (P = 0.02)								
1.1.2 Mean change in logMAR best-corrected visual acuity from baseline (6 months)								
Laursen 2004	0.02	0.21	12	0.08	0.22	11	11.5%	-0.06 [-0.24, 0.12]
Lavinsky 2011	-0.15	0.21	42	-0.07	0.15	42	58.8%	-0.08 [-0.16, -0.00]
Venkatesh 2011	0.02	0.3	23	0.08	0.26	23	13.6%	-0.06 [-0.22, 0.10]
Vujosevic 2010	0.02	0.31	32	0	0.29	30	16.1%	0.02 [-0.13, 0.17]
Subtotal (95% CI)			**109**			**106**	**100.0%**	**-0.06 [-0.12, 0.00]**
Heterogeneity: Chi² = 1.35, df = 3 (P = 0.72); I² = 0%								
Test for overall effect: Z = 1.93 (P = 0.05)								
1.1.3 Mean change in logMAR best-corrected visual acuity from baseline (9 months)								
Lavinsky 2011	-0.19	0.27	42	-0.07	0.19	42	69.9%	-0.12 [-0.22, -0.02]
Vujosevic 2010	0	0.3	32	0.01	0.31	30	30.1%	-0.01 [-0.16, 0.14]
Subtotal (95% CI)			**74**			**72**	**100.0%**	**-0.09 [-0.17, -0.00]**
Heterogeneity: Chi² = 1.41, df = 1 (P = 0.24); I² = 29%								
Test for overall effect: Z = 2.04 (P = 0.04)								
1.1.4 Mean change in logMAR best-corrected visual acuity from baseline (12 months)								
Lavinsky 2011	-0.25	0.31	42	-0.08	0.23	42	60.6%	-0.17 [-0.29, -0.05]
Vujosevic 2010	0.02	0.28	32	0.01	0.3	30	39.4%	0.01 [-0.13, 0.15]
Subtotal (95% CI)			**74**			**72**	**100.0%**	**-0.10 [-0.19, -0.01]**
Heterogeneity: Chi² = 3.60, df = 1 (P = 0.06); I² = 72%								
Test for overall effect: Z = 2.14 (P = 0.03)								

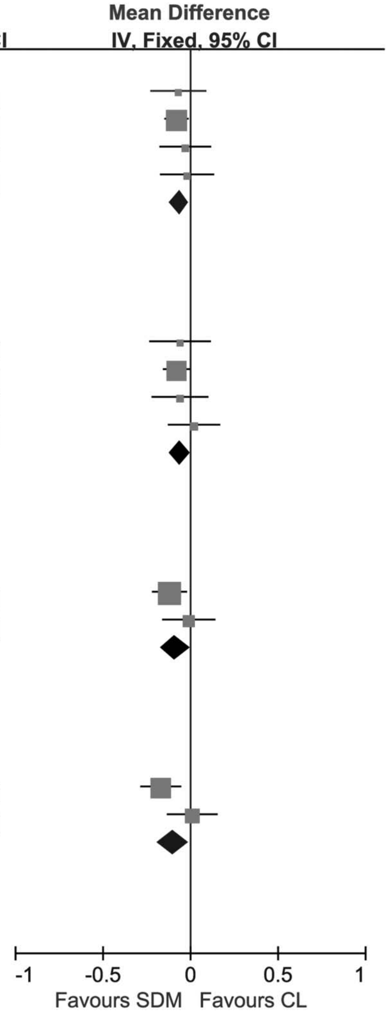

Fig. 2. Mean change in BCVA (logMAR units) from baseline comparing SDM with CL at 3, 6, 9, and 12 months after treatment. IV, inverse variance.

therapies). Focal/grid laser as a monotherapy has been the mainstay of treatment of DME until recently when results from RCTs started to indicate that the addition of anti-VEGF therapy may result in better efficacy. This was confirmed in a recent meta-analysis by our group, which indicated that intravitreal ranibizumab combined with laser is more effective compared with laser monotherapy both in terms of BCVA improvement and CMT reduction.[28] As intravitreal drug effects tend to be of rapid onset but relatively brief, whereas laser effects tend to be slower in onset but long-lasting, a combination of intraocular drug delivery and laser may be more beneficial than laser monotherapy or anti-VEGF monotherapy to selected patients with DME, particularly those presenting with severe center-involving DME. As a result of the tissue damage, inflammation and negative effect on the central visual function caused by CL, alternative therapies such as SDM represent a way to provide a better DME treatment in parallel with efforts focused on drug development. The results from the current meta-analysis support this point of view. It is worth noting that despite the inferior efficacy of laser monotherapy (either CL or SDM) compared with other treatments, it remains the only one-time event treatment option and, as such, may still be suitable for some patients who would either refuse intravitreal injections or would be anticipated to have poor compliance in view of the relatively strict treatment regimen associated with intravitreal anti-VEGF treatment. This treatment option also retains some advantage in terms of affordability, a factor especially important in developing countries.

Although the results of our meta-analysis showed a statistically significant effect on BCVA in favor of SDM at 3 and 9 months ($P = 0.02$, $P = 0.04$, respectively) and borderline significance at 6 months ($P = 0.05$), the changes in BCVA were relatively small (a mean difference of 0.06–0.09 logMAR) and thus are of limited clinical significance. Only at the 12-month follow-up did the average change in advantage to

	SDM			CL				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
1.2.1 Mean change in central macular thickness from baseline (3 months)								
Laursen 2004	0	76.1	12	26	73.66	11	9.7%	-26.00 [-87.23, 35.23]
Lavinsky 2011	-93	102	42	-67	78	42	24.0%	-26.00 [-64.83, 12.83]
Venkatesh 2011	-11.8	51.08	23	-16.9	41.27	23	50.4%	5.10 [-21.74, 31.94]
Vujosevic 2010	-17.6	105.58	32	-40.7	85.66	30	15.9%	23.10 [-24.63, 70.83]
Subtotal (95% CI)			**109**			**106**	**100.0%**	**-2.52 [-21.57, 16.52]**
Heterogeneity: Chi² = 3.39, df = 3 (P = 0.34); I² = 11%								
Test for overall effect: Z = 0.26 (P = 0.80)								
1.2.2 Mean change in central macular thickness from baseline (6 months)								
Laursen 2004	10	76.1	12	12	73.96	11	3.6%	-2.00 [-63.35, 59.35]
Lavinsky 2011	-117	119	42	-94	86	42	6.9%	-23.00 [-67.40, 21.40]
Venkatesh 2011	-23.6	57.32	23	-26.2	40.88	23	16.4%	2.60 [-26.17, 31.37]
Vujosevic 2010	-12.6	104.88	32	-51.1	87.3	30	5.9%	38.50 [-9.42, 86.42]
Xie 2013	-36.7	35.1	50	-23.7	37.1	49	67.1%	-13.00 [-27.23, 1.23]
Subtotal (95% CI)			**159**			**155**	**100.0%**	**-7.68 [-19.34, 3.98]**
Heterogeneity: Chi² = 5.08, df = 4 (P = 0.28); I² = 21%								
Test for overall effect: Z = 1.29 (P = 0.20)								
1.2.3 Mean change in central macular thickness from baseline (9 months)								
Lavinsky 2011	-144	140	42	-112	107	42	43.0%	-32.00 [-85.29, 21.29]
Vujosevic 2010	-29.4	94.5	32	-49	91.48	30	57.0%	19.60 [-26.70, 65.90]
Subtotal (95% CI)			**74**			**72**	**100.0%**	**-2.60 [-37.55, 32.36]**
Heterogeneity: Chi² = 2.05, df = 1 (P = 0.15); I² = 51%								
Test for overall effect: Z = 0.15 (P = 0.88)								
1.2.4 Mean change in central macular thickness from baseline (12 months)								
Figueira 2009	-41.9	103.8	44	-28.7	105.3	40	39.0%	-13.20 [-57.98, 31.58]
Lavinsky 2011	-154	157	42	-126	126	42	21.1%	-28.00 [-88.88, 32.88]
Vujosevic 2010	-46.6	86.36	32	-68	90.95	30	40.0%	21.40 [-22.81, 65.61]
Subtotal (95% CI)			**118**			**112**	**100.0%**	**-2.49 [-30.44, 25.46]**
Heterogeneity: Chi² = 2.02, df = 2 (P = 0.36); I² = 1%								
Test for overall effect: Z = 0.17 (P = 0.86)								

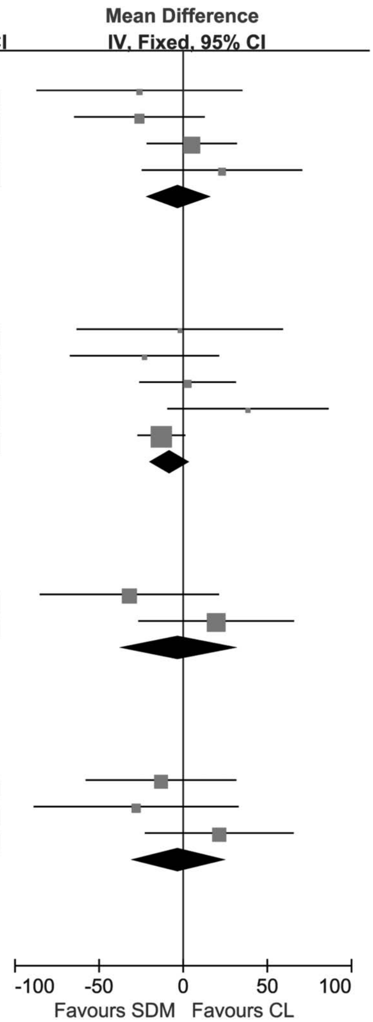

Fig. 3. Mean change in CMT (in μm) from baseline comparing SDM with CL at 3, 6, 9, and 12 months after treatment. IV, inverse variance.

SDM reach 0.1 logMAR (equivalent to one line on the ETDRS chart).

This work may have some limitations. First, we cannot fully exclude publication bias. It is possible that some works, especially those published in languages other than English may have been missed. Second, the studies were conducted with small or very small sample sizes. This factor may affect the interpretation of the results. Third, a potential source of heterogeneity is difference in BCVA values at baseline as illustrated in Table 1, which undoubtedly would have influenced the results from the treatment. For example, the two studies that followed BCVA changes up to 12 months had very different baseline BCVA values in the SDM groups: mean BCVA at the higher end of moderate vision loss of 0.90 logMAR (20/160) in Lavinsky et al[22] and substantially better mean BCVA at the lower end of mild vision loss of 0.21 logMAR (20/32) in Vujosevic et al.[24] Correspondingly, the change in BCVA as a result of treatment was much higher in former study (−0.25 logMAR) compared with practically no change in the latter study (0.02 logMAR). Another source of heterogeneity is the slightly different types of lasers used (e.g., argon vs. Nd-YAG within the CL treatment paradigm) and the different ethnic backgrounds of the patients (correlated with a different extent of fundus pigmentation and, therefore, slightly different laser absorption efficacy). Finally, all of the studies included were of relatively short follow-up period of 6 or 12 months after treatment. Thus, RCTs of longer duration and larger sample size are needed to provide more definitive information about the long-term efficacy and safety of both treatment modalities.

In conclusion, based on a limited number of studies available at the present time, the theoretical advantages of the SDM therapy over CL therapy for DME were confirmed in terms of better central visual function outcome and similar CMT outcome, thus supporting the notion that SDM is an effective therapy for the treatment of DME.

Key words: diabetic macular edema, subthreshold micropulse diode laser, photocoagulation, meta-analysis.

References

1. Frank RN. Diabetic retinopathy. N Engl J Med 2004;350:48–58.
2. Bandello F, Battaglia Parodi M, Lanzetta P, et al. Diabetic macular edema. Dev Ophthalmol 2010;47:73–110.
3. Klein R, Klein BE, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. IV. Diabetic macular edema. Ophthalmology 1984;91:1464–1474.
4. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema: early treatment diabetic retinopathy study report number 1. Arch Ophthalmol 1985;103:1796–1806.
5. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. Ophthalmology 2008;115:1447–1449.
6. Beck RW, Edwards AR, Aiello LP; Diabetic Retinopathy Clinical Research Network (DRCR net). Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema. Arch Ophthalmol 2009;127:245–251.
7. Hudson C, Flanagan JG, Turner GS, et al. Influence of laser photocoagulation for clinically significant diabetic macular oedema (DMO) on short-wavelength and conventional automated perimetry. Diabetologia 1998;41:1283–1292.
8. Schatz H, Madeira D, McDonald HR, Johnson RN. Progressive enlargement of laser scars following grid laser photocoagulation for diffuse diabetic macular edema. Arch Ophthalmol 1991;109:1549–1551.
9. Lewis H, Schachat AP, Haimann MH, et al. Choroidal neovascularization after laser photocoagulation for diabetic macular edema. Ophthalmology 1990;97:503–510.
10. Guyer DR, D'Amico DJ, Smith CW. Subretinal fibrosis after laser photocoagulation for diabetic macular edema. Am J Ophthalmol 1992;113:652–656.
11. Striph GG, Hart WM Jr., Olk RJ. Modified grid laser photocoagulation for diabetic macular edema. The effect on the central visual field. Ophthalmology 1988;95:1673–1679.
12. Roider J. Laser treatment of retinal diseases by subthreshold laser effects. Semin Ophthalmol 1999;14:19–26.
13. Yu AK, Merrill KD, Truong SN, et al. The comparative histologic effects of subthreshold 532- and 810-nm diode micropulse laser on the retina. Invest Ophthalmol Vis Sci 2013;54:2216–2224.
14. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6:e1000100.
15. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12.
16. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–560.
17. Neely JG, Magit AE, Rich JT, et al. A practical guide to understanding systematic reviews and meta-analyses. Otolaryngol Head Neck Surg 2010;142:6–14.
18. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–1101.
19. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315: 629–634.
20. Figueira J, Khan J, Nunes S, et al. Prospective randomised controlled trial comparing sub-threshold micropulse diode laser photocoagulation and conventional green laser for clinically significant diabetic macular oedema. Br J Ophthalmol 2009; 93:1341–1344.
21. Laursen ML, Moeller F, Sander B, Sjoelie AK. Subthreshold micropulse diode laser treatment in diabetic macular oedema. Br J Ophthalmol 2004;88:1173–1179.
22. Lavinsky D, Cardillo JA, Melo LA Jr, et al. Randomized clinical trial evaluating mETDRS versus normal or high-density micropulse photocoagulation for diabetic macular edema. Invest Ophthalmol Vis Sci 2011;52:4314–4323.
23. Venkatesh P, Ramanjulu R, Azad R, et al. Subthreshold micropulse diode laser and double frequency neodymium: YAG laser in treatment of diabetic macular edema: a prospective, randomized study using multifocal electroretinography. Photomed Laser Surg 2011;29:727–733.
24. Vujosevic S, Bottega E, Casciano M, et al. Microperimetry and fundus autofluorescence in diabetic macular edema: subthreshold micropulse diode laser versus modified early treatment diabetic retinopathy study laser photocoagulation. Retina 2010;30:908–916.
25. Xie TY, Guo QQ, Wang Y, et al. Randomized, controlled clinical trial comparision of SDM laser versus argon ion laser in diabetic macular edema. Guoji Yanke Zazhi (int Eye Sci) 2013;13:2370–2372.
26. Luttrull JK, Dorin G. Subthreshold diode micropulse laser photocoagulation (SDM) as invisible retinal phototherapy for diabetic macular edema: a review. Curr Diaberes Rev 2012;8: 217–284.
27. Maeshima K, Utsugi-Sutoh N, Otani T, Kishi S. Progressive enlargement of scattered photocoagulation scars in diabetic retinopathy. Retina 2004;24:507–511.
28. Chen G, Li W, Tzekov R, et al. Ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema: a meta-analysis of randomized controlled trials. PLoS One 2014;9:e115797.