Original Article

Efficacy and safety of triamcinolone acetonide injection combined with laser photocoagulation in the treatment of diabetic macular edema: a systematic review and meta-analysis

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Background: Diabetic macular edema (DME) is a type of retinopathy caused by diabetes, and the 2 main clinical treatment modalities are drug therapy intravitreal triamcinolone acetonide injection (IVTA) and laser photocoagulation. This meta-analysis investigated the efficacy of combining both the 2 treatment modalities.

Methods: The Embase, Cochrane library, PubMed, and Ovid databases were searched for English literatures. The literatures were screened and assessed for the risk of bias, after that the Revman 5.4 software was used to conduct the meta-analysis.

Results: A total of 8 articles, including 549 patients, were included in this study. Meta-analysis showed that the effect of (IVTA + laser) on early central macular thickness (CMT) was not significantly different with IVTA alone [mean difference (MD) =−5.13, 95% confidence interval (CI): −17.06 to 6.80, P=0.40], however, significantly different with laser alone (MD =−94.31, 95% CI: −135.04 to −53.58, P<0.00001). Similarly, the effect of (IVTA + laser) on early best corrected visual acuity (BCVA) was not significantly different with IVTA alone (MD =0.02, 95% CI: −0.03 to 0.07, Z=0.79, P=0.43). but different with laser alone [MD =−0.20, 95% CI: −0.24 to −0.16, Z=10.16, P<0.00001). The effect of (IVTA + laser) on long-term CMT was not significantly different with IVTA alone (MD =−66.90, 95% CI: −132.66 to −1.15, Z=1.99, P=0.05) nor with laser alone (MD =−15.86, 95% CI: −31.37 to −0.35, Z=2.00, P=0.05). Similarly, the effect of combined intervention (IVTA + laser) on long-term BCVA was not significantly different with IVTA alone (MD =−0.18, 95% CI: −0.39 to 0.03, Z=1.71, P=0.09) nor with laser alone (MD =−0.11, 95% CI: −0.23 to 0.01, Z=1.74, P=0.08). Administration of IVTA before laser was superior to laser alone (MD =−0.19, 95% CI: −0.31 to −0.07, Z=3.09, P=0.002).

Discussion: The effect of IVTA + laser therapy is similar to IVTA alone, but superior to laser alone for the early treatment of DME. However, the long-term effect is similar to IVTA alone or laser alone, a better therapeutic effect can be achieved if IVTA is administered before laser treatment.

Keywords: Intravitreal triamcinolone acetonide (IVTA); laser photocoagulation; diabetic macular edema (DME); meta-analysis

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Introduction

Diabetic macular edema (DME) is a type of retinopathy associated with diabetes. It is caused by abnormal accumulation of retinal extracellular fluid due to changes in ocular microcirculation as a result of the long-term hyperglycemic state in diabetic patients (1). Macular edema accounts for approximately 14% of all diabetic retinopathies (2). The degree of macular edema is related to the course of diabetes, the longer the course of disease, the more severe the macular edema. The pathophysiological basis is that persistent hyperglycemia can cause retinal hypoxia and produce vascular endothelial growth factor (VEGF), which is on kind of inflammatory factor that can destroy connexin, thereby damaging the blood retinal barrier, and accelerating endothelial cell apoptosis and increasing vascular permeability, causing effusion and cell swelling (3). At present, the main forms of treatment for macular edema include intravitreal injection of drugs such as ranibizumab, aflibercept, and triamcinolone acetonide, and laser photocoagulation techniques (3). Macular laser photocoagulation (MLP) plays an important role in the treatment of DME too, it can increase the oxidation of inner retina through thermal effect, so as to inhibit the production of VEGF, also it can shrink retinal blood vessels, reduce intravascular pressure and permeability, and improve retinal barrier function, so as to reduce macular edema and improve vision(4). Intravitreal injection of triamcinolone acetonide (IVTA) can reduce the penetration of inflammatory vessels and regulate the expression of vascular endothelial growth factor, thereby reducing macular edema and improving visual acuity without increasing the incidence of elevated intraocular pressure and lens opacity comparing to MLP (5). In a meta-analysis conducted by Liu *et al.* (6), the RCTs concerning MLP with or without IVTA pretreatment for DME were retrieved, it was concluded that MLP with IVTA pretreatment has a better therapeutic effect in terms of CMT reduction compared with MLP alone. However, the study lacked the comparison between the combination method and IVTA alone, which made the meta-analysis not comprehensive enough. Our meta-analysis evaluated the early and long-term effects of combined therapy with both IVTA alone and MLP alone to provide a reference for the treatment of clinical DME. We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/apm-21-3274).

Methods

Database and search strategy

The Embase, Cochrane library, PubMed, and Ovid databases were searched for all English literatures relating to the treatment of DME published between January 2000 and January 2021. The search keywords were intravitreal triamcinolone acetonide (IVTA) injection, macular laser photocoagulation, and DME. We only included English literatures because we believed the quality of English literatures are better.

Literature inclusion criteria

Studies were included if all patients had significant macular edema in the affected eye observable under the biomicroscope, with macular thickening as the main feature. Angiography should show diffuse fluorescein leakage, without microaneurysm reaction. Optical coherence tomography should show increased central macular thickness (CMT) (>250 μm). All patients should have a long-term history of longuria (type 1 or type 2 diabetes) and have been clinically diagnosed with DME. Non-diabetes-induced macular edema such as proliferative retinopathy, glaucoma and ocular hypertension, and ischemia-induced macular edema were excluded. Patients must have not received laser photocoagulation within 3 months nor any other ophthalmic surgery within 6 months.

The intervention measures used in the studies should include at least 2 groups of relative contrast. One group must be treated with IVTA injection combined with macular laser photocoagulation (MLG) and the control groups should be IVTA alone or MLG alone. The observation time after intervention should be at least 3 months. At least one rehabilitation index [CMT or best corrected visual acuity (BCVA)] should be included and complete data should be available in the form of mean ± standard deviation.

Exclusion criteria of literatures

Studies in which the intervention was intravitreal injection of ranibizumab, atracept, or any other non-triamcinolone acetonide drugs, or the combined intervention measures did not include laser photocoagulation were excluded. Non-randomized controlled studies were not included in this meta-analysis. Investigations that did not include a rehabilitation indicator, or studies with the data not

retrieved or transformed were also excluded. Literature for which the original text could not be obtained were excluded.

Literature screening

Literatures retrieved from the database searches were independently reviewed by 2 researchers and filtered based on the inclusion and exclusion criteria. Duplicate literatures were excluded.

Literature quality evaluation and bias risk assessment

The Cochrane Handbook for Systematic Reviews of Intervention was used for literature quality evaluation and risk of bias evaluation. The 6 aspects of the evaluation were as follows: (I) randomization method; (II) blinding method; (III) implementation of allocation concealment; (IV) data integrity; (V) selective reporting bias; and (VI) other biases. These were assessed as "low risk", "unclear", and "high risk". If the literature was evaluated as low risk in all 6 aspects, it would be considered level A study. If there was 1 or more "unclear" assessment, the study would be considered a level B literature. If there was one or more "high risk" evaluation, the study would be classified as level C literature.

Outcome indicators

The main outcome indicators were early CMT, BCVA, long-term CMT, and long-term BCVA. The secondary indicators were intraocular pressure, pain, and adverse reactions.

Data extraction

Two researchers independently collated the following data from the included literatures: author, year and month of publication, the number of groups, age, gender ratio, intervention indicators, intervention frequency, observation time, and rehabilitation indicators. Any discrepancies between the researchers were resolved by discussion. The corresponding authors were contacted for any missing data, and if the data still could not be obtained, the study would be excluded for analysis.

Statistical methods

Meta-analysis was performed using the Revman 5.4 software. Continuous variables (CMT and BCVA) were analyzed by inverse variance statistics and reported using weighted mean deviation (WMD) and 95% confidence intervals (CIs). Forest plot descriptive statistics were used for representation of the results. Outcome indicators which were reported by 3 or more studies were comprehensively analyzed, otherwise the meta-analysis of that particular indicator would be omitted. Literature heterogeneity was detected by I^2 statistics and Q validation, where $I^2>50\%$ or $P<0.1$ indicated heterogeneity of the results. If there was significant heterogeneity among literatures, the random effects model analysis was used, otherwise the fixed effects model was applied. If there was heterogeneity between literatures, the heterogeneity investigation was conducted by eliminating studies one by one. Sensitivity analysis was performed by comparing the random effects results with the fixed effect results. Funnel plots were used to assess publication bias.

Results

Literature screening

Figure 1 shows the literature selection process. Finally, 8 articles, with a total of 549 patients, were included in this quantitative analysis. The basic characteristics, patient information, intervention indicators, follow-up time, and main outcome measures collated from the included literatures are shown in *Tables 1,2*.

Literature quality and bias evaluation

In this study, all literatures described the generation method of random sequence (most did not describe which random method was used), all described the allocation concealment method (most did not describe the specific concealment method), none described the implementation details of the blinding method, all recorded the drop-out cases in detail and these cases were excluded from the final results. There was no significant selective reporting bias nor any other bias. The overall quality was moderate. The results are shown in *Table 3*.

Meta-analysis results

The effects of different intervention methods on early central macular thickness (1 month after treatment)

A total of 3 literatures (8-10) reported the effects of combined intervention and IVTA intervention on early

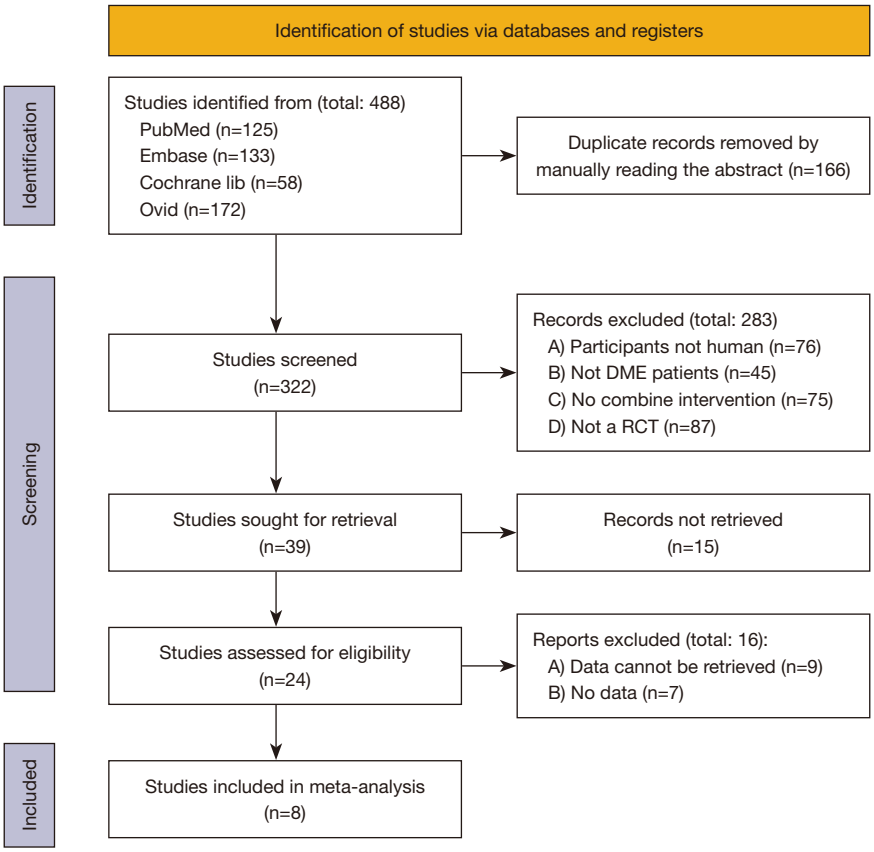

Figure 1 A flow chart showing the literature selection process.

CMT. There was no statistical heterogeneity among the 3 studies (I^2=0%; P=0.90) , and the fixed effects model was used. Meta-analysis showed that the effect of combined intervention (IVTA + laser) on early CMT was not significantly different from IVTA treatment alone (MD =–5.13, 95% CI: –17.06 to 6.80, Z=0.84, P=0.40; *Figure 2*).

A total of 5 literatures (8,10,11,13,14) reported the effects of combined intervention and laser intervention alone on early CMT, and the heterogeneity between the studies was statistically significant (I^2=89%, P<0.00001). Using the random-effects model, the meta-analysis showed that combined intervention (IVTA + laser) significantly reduced the early CMT compared with laser treatment alone (MD =–94.31, 95% CI: –135.04 to –53.58, Z=4.54, P<0.00001; *Figure 3*).

The effects of different intervention methods on early best corrected visual acuity (1 month after treatment)

A total of 3 literatures (8-10) compared the effects of combined intervention and IVTA intervention on early BCVA. There was no statistical heterogeneity among the 3 literatures (I^2=0%, P=0.50) and the fixed effects model was used. Meta-analysis showed that the effects of combined intervention (IVTA + laser) on early BCVA was not significantly different from IVTA treatment alone (MD =0.02, 95% CI: –0.03 to 0.07, Z=0.79, P=0.43; *Figure 4*).

A total of 5 literatures (8,10,11,13,14) compared the effects of combined intervention and laser intervention alone on early BCVA. There was no statistical heterogeneity among the 5 studies (I^2=33%, P=0.20) and the fixed effects model was used. Meta-analysis showed that combined intervention (IVTA + laser) significantly improved early BCVA compared with laser intervention alone (MD =–0.20, 95% CI: –0.24 to –0.16, Z=10.16, P<0.00001; *Figure 5*).

The effects of different intervention methods on long-term central macular thickness (6 or 12 months after treatment)

A total of 4 literatures (7-10) compared the effects of combined intervention and IVTA intervention alone on

Table 1 The basic characteristics, patient information, intervention measures, and follow-up time of the included literatures

Author and date of publication	Grouping	Age (years)	Number of affected eyes	Interventions	Intervention sequence (IVTA, Laser)	Follow-up time (months)
Cho *et al.* (7), 2012	Combined group	59.28±8.99	48	IVTA + laser	Before	6
	IVTA group	58.15±9.75	38	IVTA	–	
Lam *et al.* (8), 2007	Combined group	–	36	IVTA + laser	Before	6
	IVTA group	–	38	IVTA	–	
	Laser group	–	37	Laser	–	
Kang *et al.* (9), 2006	Combined group	61.1±9.3	48	IVTA + laser	Before	6
	IVTA group	57.4±10.6	38	IVTA	–	
Lee *et al.* (10), 2009	Combined group	63.6±11.1	30	IVTA + laser	After	6
	Laser group	59.6±10.8	28	Laser	–	
	IVTA group	–	20	IVTA	–	
Parodi *et al.* (11), 2008	Combined group	70.9	11	IVTA + laser	After	12
	Laser group	65.2	13	Laser	–	
Aydin *et al.* (12), 2009	Combined group	61.8±8.2	17	IVTA + laser	Before	6
	IVTA group	59.2±8.7	19	IVTA	–	
Gillies *et al.* (13), 2011	Combined group	65.4±9.5	42	IVTA + laser	Before	12
	Laser group	66.9±8.9	42	Laser	–	
Maia Jr *et al.* (14), 2009	Combined group	61.9±5.3	22	IVTA + laser	After	12
	Laser group	62.3±5.9	22	Laser	–	

IVTA, intravitreal triamcinolone acetonide.

Table 2 Intervention indicators and reported literatures

Outcome indicators	Units	Reported literatures
Early CMT	μm	(8-11,13,14)
Early BCVA	LogMAR	(8-11,13,14)
Long-term CMT	Low	(7-11,13,14)
Long-term BCVA	Low	(7-14)
Complications	N/%	(7,8)

CMT, central macular thickness; BCVA, best corrected visual acuity; logMAR, logarithm of the minimum angle of resolution.

long-term CMT, and there was statistical heterogeneity among the 4 studies (I^2=84%, P=0.0002). The random effects model was used and meta-analysis revealed that the effects of combined intervention (IVTA + laser) on long-term CMT was not significantly different from IVTA intervention alone (MD =−66.90, 95% CI: −132.66 to −1.15, Z=1.99, P=0.05; *Figure 6*).

A total of 5 literatures (8,10,11,13,14) compared the effects of combined intervention and laser intervention alone on long-term CMT, and there was statistical heterogeneity among the studies (I^2=58%, P=0.05). The random effects model was used and meta-analysis showed no significant difference between combined intervention (IVTA + laser) and laser alone treatment on long-term

Table 3 Risk of bias and quality assessment based on the Cochrane Handbook for Evaluation of Randomized Interventions

Study	Random sequence generation	Classification hiding	Blind method	Data integrity	Optional reporting	Other bias	Grade
Cho *et al.* (7), 2012	Low	Low	Unclear	Low	Low	Low	Class B
Lam *et al.* (8), 2007	Low	Low	Unclear	Low	Low	Low	Class B
Kang *et al.* (9), 2006	Low	Low	Unclear	Low	Low	Low	Class B
Lee *et al.* (10), 2009	Low	Low	Unclear	Low	Low	Low	Class B
Parodi *et al.* (11), 2008	Low	Low	Unclear	Low	Low	Low	Class B
Aydin *et al.* (12), 2009	Low	Low	Unclear	Low	Low	Low	Class B
Gillies *et al.* (13), 2011	Low	Low	Unclear	Low	Low	Low	Class B

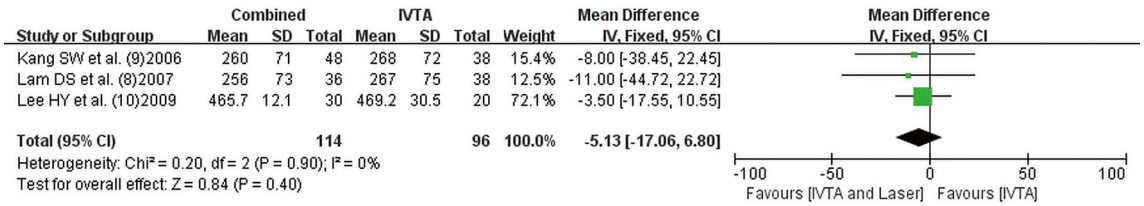

Figure 2 The effects of combined treatment versus IVTA alone on early central macular thickness. IVTA, intravitreal triamcinolone acetonide.

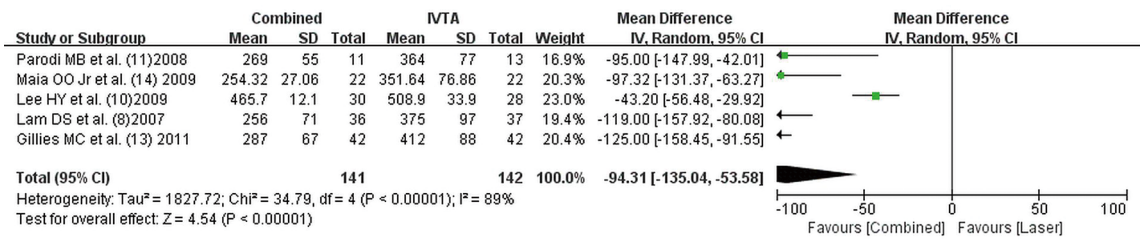

Figure 3 The effects of combined treatment versus laser treatment alone on early central macular thickness.

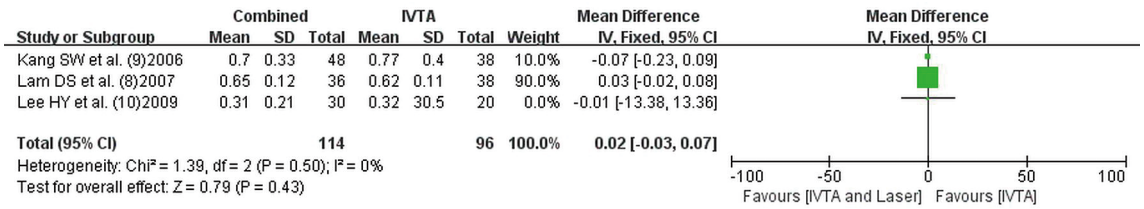

Figure 4 The effects of combined treatment versus IVTA alone on early BCVA. IVTA, intravitreal triamcinolone acetonide; BCVA, best corrected visual acuity.

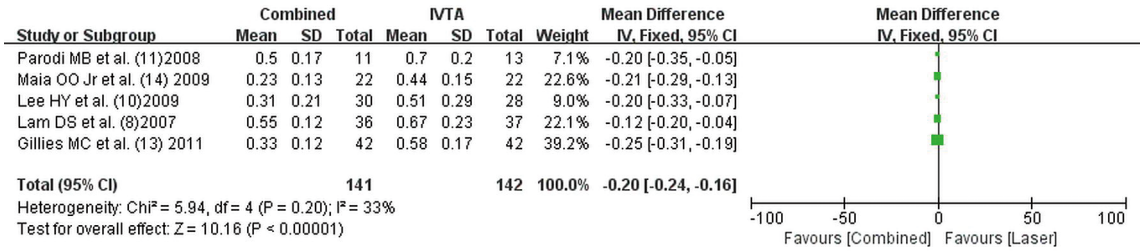

Figure 5 The effects of combined treatment versus laser treatment alone on early BCVA. BCVA, best corrected visual acuity.

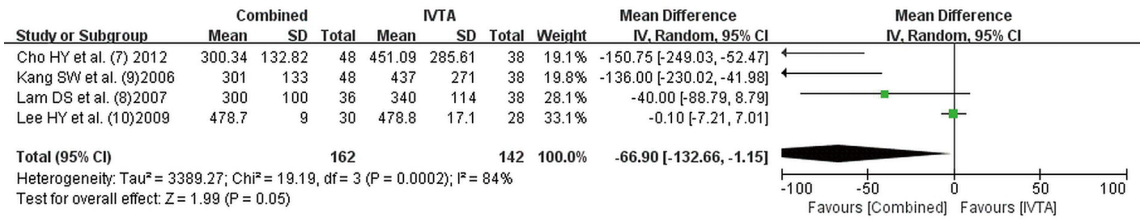

Figure 6 The effects of combined treatment versus IVTA treatment alone on long-term central macular thickness. IVTA, intravitreal triamcinolone acetonide.

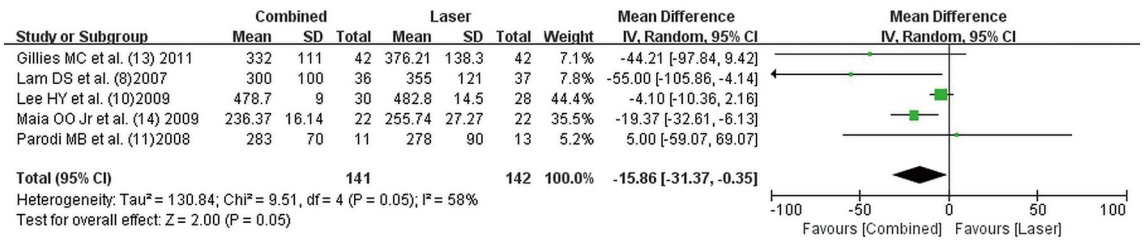

Figure 7 The effects of combined treatment versus laser treatment alone on long-term central macular thickness.

CMT (MD =−15.86, 95% CI: −31.37 to −0.35, Z=2.00, P=0.05; *Figure 7*).

The effects of different intervention methods on long-term best corrected visual acuity (6 or 12 months after treatment)

A total of 5 literatures (7-10,12) reported on the effects of combined intervention and IVTA intervention alone on long-term BCVA, with statistical heterogeneity among the 5 studies (I^2=85%, P=0.0002). The random effects model was used and meta-analysis demonstrated that the effects of combined intervention (IVTA + laser) on long-term BCVA was not significantly different from that observed with IVTA treatment alone (MD =−0.18, 95% CI: −0.39 to 0.03, Z=1.71, P=0.09; *Figure 8*).

There were 5 literatures (8,10,11,13,14) that reported the effects of combined intervention and laser intervention alone on long-term BCVA. There was statistical heterogeneity among the 5 reports (I^2=84%, P<0.0001). Using the random effects model, meta-analysis found no significant difference between combined intervention (IVTA + laser) and laser intervention alone on long-term BCVA (MD =−0.11, 95% CI: −0.23 to 0.01, Z=1.74, P=0.08; *Figure 9*).

Analysis of complications

One study (7), reported elevated intraocular pressure in 9 patients (34.6%) treated with IVTA and 8 patients (21.6%) who underwent combined treatment, and this was resolved after local drug treatment. Another study (8) reported elevated intraocular pressure in 2 (5%), 14 (37%), and 13 (36%) patients in the laser alone, IVTA alone, and combined treatment groups, respectively.

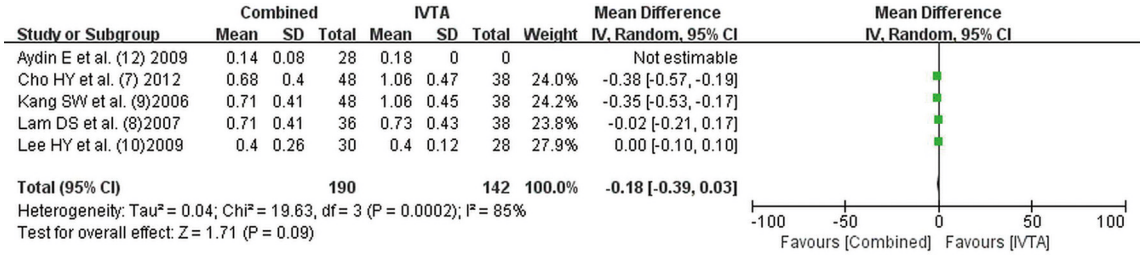

Figure 8 The effects of combined treatment versus IVTA treatment alone on long-term BCVA. IVTA, intravitreal triamcinolone acetonide; BCVA, best corrected visual acuity.

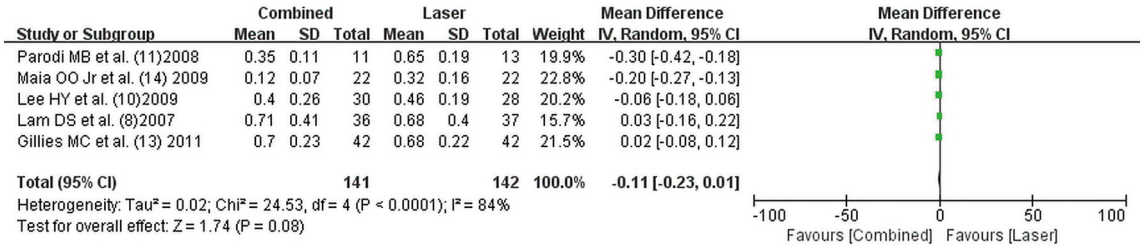

Figure 9 The effects of combined treatment versus laser treatment alone on long-term BCVA. BCVA, best corrected visual acuity.

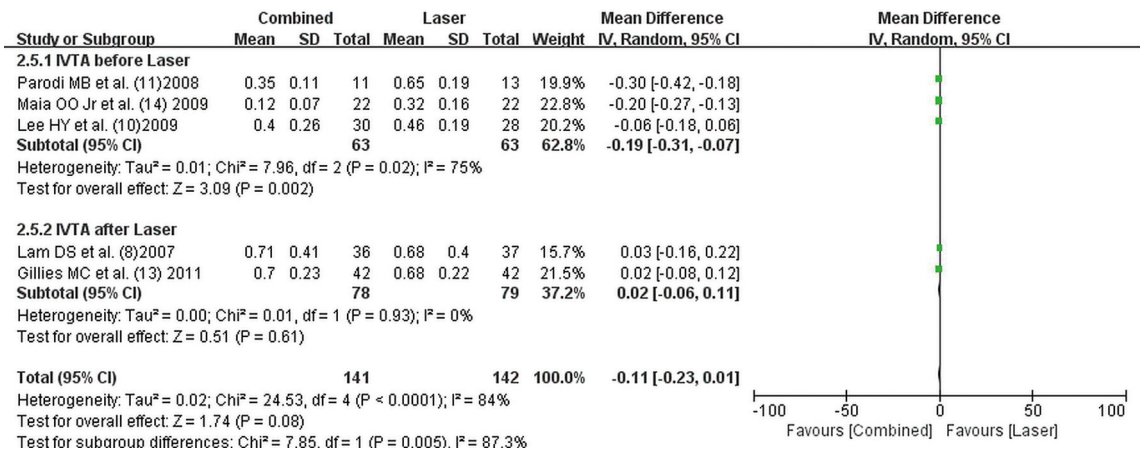

Figure 10 Subgroup analysis of IVTA before and after laser treatment compared to laser therapy alone. IVTA, intravitreal triamcinolone acetonide.

Subgroup analysis

Subgroup analysis showed that administering IVTA before laser treatment had a significant effect on long-term BCVA compared to laser treatment alone (MD =–0.19, 95% CI: –0.31 to –0.07, *Z*=3.09, P=0.002). However, administration of IVTA after laser treatment showed no significant difference in long-term BCVA compared to laser treatment alone (P=0.61, *Figure 10*).

Heterogeneity investigation and sensitivity analysis

The source if heterogeneity in *Figure 3* was examined by eliminating each study one by one. When the study by Lee *et al.* (10) was excluded, the remaining 4 literatures showed no statistical heterogeneity (I^2=0%, P=0.61), indicating that the former study (10) was the source of heterogeneity. In the study by Lee *et al.* (10), the initial macular thickness of the patients was higher than that reported in other studies, and

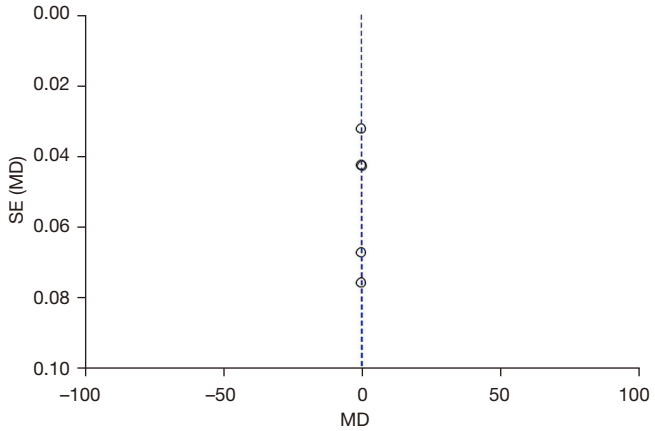

Figure 11 Funnel plot analysis of publication bias.

the disease severity was also greater, and this might have caused the heterogeneity. The random effects model and the fixed effects model were used for the meta-analysis in *Figure 2*. There was no significant difference in the results between the 2 groups, indicating that the results had no significant sensitivity and good stability.

Analysis of publication bias

The funnel plot based on the meta-analysis in *Figure 5* showed that both groups of studies were close to the midline, suggesting that the possibility of publication bias was small (*Figure 11*).

Discussion

Laser treatment acts on the retinal pigment epithelial layer to repair the blood-retinal barrier and reduce the oxygen demand in the inner retinal layer, thereby reducing edema (15). Triamcinolone acetonide is a glucocorticoid that can effectively stabilize the blood-retinal barrier, inhibit the expression of vascular endothelial growth factor (VEGF), and reduce vascular permeability, thereby eliminating edema, reducing DME symptoms, and improving visual acuity (16). Comparisons of the efficacy of the 2 modalities of treatment for DME have been controversial. In a study led by the Diabetic Laser Retinopathy Clinical Research Network (17), 693 patients participated in a 2-year study, and the results showed that laser photocoagulation treatment was more effective and had fewer sides effects than IVTA. However, a meta-analysis (6) of 7 literatures with a total of 540 patients showed that after 1 month of treatment, patients treated with IVTA experienced better recovery in terms of visual acuity compared to patients treated with laser photocoagulation.

This current meta-analysis, involving 8 literatures and 549 patients, compared the early and long-term therapeutic effects (CMT and BVCA) of combined IVTA and laser treatment (IVTA + laser) with IVTA treatment alone or laser treatment alone. The results demonstrated that in terms of early therapeutic effects, IVTA + laser was not superior to IVTA treatment alone, but had better therapeutic effects compared to laser alone treatment. However, long-term efficacy was not significantly different between IVTA + laser and either IVTA alone nor laser alone. This suggested that the early therapeutic effects of IVTA was superior to that of laser treatment, which was consistent with the conclusions reported by Hong IH and colleagues (16). Our current study did not directly compare the long-term effects of the 2 treatment methods, it was unable to distinguish between the advantages and disadvantages of the methods (this was not the purpose of this meta-analysis). However, it can be seen from the results that the combined treatment modality is not only characterized by rapid improvement of macular edema symptoms in patients in the early stages of IVTA, but it can also achieve the same therapeutic effect as laser photocoagulation in the long term. Overall, the combination treatment did not show an additive effect of the 2 individual treatment regimens. But it is worth noting that in the combined treatment modality, administration of IVTA before laser treatment showed a better therapeutic effect compared to laser photocoagulation alone, suggesting that administration of IVTA followed by laser treatment not only achieves good early results, but can also result in better long-term efficacy. However, only 63 eyes were included in this comparison and further controlled clinical studies are warranted to verify these results. Since the early or long-term efficacy of combination therapy has not increased comparing to each one of the therapies alone, we believe that any one of the two treatment methods can be selected under the condition of the patient can well tolerate it.

Cho *et al.* (7) and Lam *et al.* (8) noted that the main adverse reactions of combined treatment was elevated intraocular pressure, which had a rate no more than IVTA alone or laser alone, and could be reversed with appropriate nursing support. Other studies (18) have reported that IVTA treatment may cause glaucoma and cataract, however, this was not observed in the current study.

A total of 8 literatures were included in the meta-analysis.

Since the number of study subjects was relatively small and some literatures did not describe the blinding method, this may have caused some implementation bias. Therefore, future randomized controlled trials are warranted to further explore the application of IVTA and laser photocoagulation in patients with DME.

Conclusions

Combination therapy involving IVTA and laser photocoagulation is superior to laser photocoagulation alone in the treatment of early DME. However, the long-term effects are similar to IVTA alone or laser photocoagulation alone. In combination therapy, better therapeutic effects can be achieved when IVTA is administered prior to laser treatment.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-3274

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-3274). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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