·Meta-Analysis·

Macular laser photocoagulation with or without intravitreal triamcinolone pretreatment for diabetic macular edema: a result from five randomized controlled trials

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Abstract

• AIM: To assess possible benefits of intravitreal triamcinolone acetonide (IVTA) injection as pretreatment for macular laser photocoagulation (MLP) in patients with diabetic macular edema (DME).

• METHODS: Published randomized controlled trials (RCTs) concerning MLP with or without IVTA pretreatment for DME were retrieved from databases CNKI, Medline, EMbase, Web of Science, and the Cochrane Library. A Meta-analysis on eligible studies was conducted using RevMan 5.0 software. Two investigators independently assessed the quality of the trials and extracted data. Main outcome measures included the change in best-corrected visual acuity (BCVA), difference in central macular thickness (CMT) and adverse events reporting in particular elevated intraocular pressure within the follow-up period. The results were pooled using weight mean difference (WMD) or odds risk (OR) with their corresponding 95% confidence intervals (CI). A fixed- or random-effect model was employed depending on the heterogeneity of the inclusion trials.

• RESULTS: Finally, five independent RCTs were identified and used for comparing MLP with IVTA pretreatment (131 eyes) with MLP alone (133 eyes, control group). The overall study quality was relatively higher according to the modified Jadad scale. The Meta-analysis showed that MLP with IVTA pretreatment significantly reduced CMT at one, three and six months (P=0.002, 0.0003 and 0.04, respectively), compared with MLP alone. The IVTA pretreatment group showed statistically significant improvements in BCVA at the one-month follow up as compared with the control group (P=0.03). At three- and six-month follow up, there was a beneficial trend towards improving visual acuity in the IVTA pretreatment group without statistical significance between groups (P=0.06 and 0.20, respectively). The incidence of elevation of intraocular pressure was significantly higher in the IVTA pretreatment group than in the control group (P<0.0001). No evidence of publication bias was present according to Begg´s test and Egger´s test. There was a low level of heterogeneity in the included studies.

• CONCLUSION: This Meta-analysis indicates that MLP with IVTA pretreatment has a better therapeutic effect in terms of CMT reduction and earlier (1mo) visual improvement for patients with DME as compared with MLP alone. Further confirmation with rigorously well-designed multi-center trials is needed.

• KEYWORDS: photocoagulation; intravitreal injection; triamcinolone acetonide; diabetic macular edema

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INTRODUCTION

Diabetic macular edema (DME) is a common microvascular complication and the principle cause of visual impairment in patients with diabetes [1]. Although macular laser photocoagulation (MLP) is a gold standard therapy for DME, laser photocoagulation on an edematous macula is not just technically more difficult but also less effective to achieve its desired result. However, intravitreal triamcinolone acetonide (IVTA) injection can induce regression of macular edema by reducing the breakdown of the blood-retina barrier in patients with diabetes[2]. Therefore, it was suggested that reduction of macular edema by pretreatment of IVTA injection first may render macular laser treatment easier and achieve a better result. Recently, numerous studies have reported clinical outcomes of laser photocoagulation combined with IVTA injection in the management of DME[3-8].

Although many investigators perform IVTA injection before macular photocoagulation in diabetic patients with macular edema, systematic or larger sample studies illustrating its benefits in facilitation of macular photocoagulation and clinical outcomes are limited. Therefore, it is necessary to review in greater depth the available data to understand the benefits of IVTA pretreatment. In an attempt to demonstrate the benefits in efficacy and safety as the primary comparative criteria, we performed a systemic review and Meta-analysis of randomized controlled trials (RCTs) involving MLP combined with pretreatment of IVTA injection compared to MLP alone for the treatment of DME.

MATERIALS AND METHODS

Search Strategy An electronic search of the literature was performed by two experienced reviewers (Liu XD and Zhou XD) employing the following databases: CNKI, Medline, EMbase, Web of Science, and the Cochrane Central Register of Controlled Trials. There were no language restrictions on the publications and all was up to the 31 October 2014. For maximum sensitivity, the search strategy was based on the combinations of medical subject headings and free text words. The following search terms were used during the searches: "laser", "photocoagulation", "triamcinolone", and "diabetic macular edema". When titles and/or abstracts fit the objectives, the full article would be retrieved. The reference lists of every retrieved article and previous systematic review were scrutinized to identify additional trials not included in the electronic databases. Any discordance about study inclusion between the two reviewers was resolved by following a discussion until a consensus was reached on the final interpretation of the data.

Inclusion and Exclusion Criteria Articles potentially eligible for inclusion in this Meta-analysis were RCTs comparing MLP combined with IVTA pretreatment with MLP alone for the treatment of DME published up to the 31 October 2014. And the outcome measures included at least one of the followings: best-corrected visual acuity (BCVA) logarithm of the minimum angle of resolution (logMAR) units, central macular thickness (CMT) measured by optical coherence tomography (OCT), and adverse events.

The following criteria were used to exclude articles for the Meta-analysis: 1) macular edema secondary to causes other than diabetic maculopathy; 2) triamcinolone acetonide was not used as an intravitreal injection; and 3) coexisting proliferative diabetic retinopathy. In addition, articles were also excluded if they did not satisfy one or more inclusion criteria. In this analysis, only the data from the longest period of follow up were used to avoid duplication if same patient populations were reported in several publications.

Data Extraction Data for study characteristics and clinical treatment were summarized and incorporated into table format by the two reviewers. And the following data were extracted from all included studies using a predefined form: 1) basic information from papers such as: year of publication, region and author name *etc*; 2) characteristics of patients such as: median age, gender, and type of DME; 3) information of study designation such as: sample size per-group, study design, randomization scheme, inclusion criteria, and type of outcome measures used; and 4) information of treatment such as: treatment regimen, dose of triamcinolone acetonide, withdrawals, CMT, BCVA, adverse events and so on. When necessary, we attempted to contact investigators directly to seek missing data not included in the published manuscripts. In case of conflicting evaluations, the disagreements were adjudicated by discussion among the whole group members to validate the accuracy of extraction.

Quality Assessment of Included Studies The same reviewers independently assessed the methodological quality of included studies according to the modified Jadad standards[9]. Parameters judging the quality included allocation concealment, the method of intervention allocation, the degree of masking, and the completeness in subject follow-up. The overall scores range from 0 to 7. Scores of 0-3 and 4-7 were regarded as low and high scores, respectively. Disagreements were also settled down by following a discussion among authors.

Statistical Analysis The analysis was undertaken on an intention-to-treat basis: patients were analyzed according to treatment allocated, irrespective of whether they received that treatment. Statistical analysis of the pooled weight mean difference (WMD) for CMT and BCVA, and the pooled odds ratio (OR) for adverse events was calculated using the Review Manager 5.0 software. All confidence intervals (CIs) had a two-sided probability coverage of 95%. A P value of <0.05 was considered statistically significant. Statistical heterogeneities were estimated using Chi-square based Q statistic with a P-value <0.1 as statistically significant heterogeneity. We also quantified the effect of heterogeneity by using the I^2 test (ranges from 0 to 100%). A significant Chi-square based Q test with P <0.1 or I^2>50% indicated that heterogeneity among studies existed. The random-effect model was conducted for Meta-analysis. Otherwise, the fixed-effect model was used. A sensitivity analysis was performed by excluding the studies with low quality (Jadad score ≤3). The funnel plots, Begg's rank correlation test[10] and Egger's linear regression test [11] were used to assess the publication biases, with P<0.05 indicating potential bias.

RESULTS

Characteristics of the Eligible Studies The process of selecting studies for the Meta-analysis is shown in Figure 1. Eventually, five randomized controlled trials published 2005 and 2011 met the inclusion criteria [5,12-15], and a search of the article references did not produce additional relevant publications. Among them, all the studies reported CMT and

Table 1 Characteristics of trials included in the Meta-analysis

Trials (first author, year)	Trial design	Region	Original patients (eyes)	Dropout patients (eyes)	Mean age±SD (rang, a) (M/F)	System baselines	Ocular baselines	Duration (mo)	Jadad score
Avitabile[12],2005	RCT	Italy	[1](15) [2](16)	0	Total:64 (55-72)	NS: DM duration, systematic hypertension	NS: lens status, VA, CMT, IOP	9	5
Lam[13], 2007	RCT	China	[1]36(36) [2]37(37)	0	[1]64.7±10.3 (21/15) [2]66.2±8.2 (15/22)	NR	NS: lens status, VA, CMT, IOP, previous laser	6	5
Lee[14], 2009	RCT	Korea	[1]26(30) [2]28(30)	0	[1]63.6±11.1 (10/16) [2]59.6±10.8 (12/16)	NS: DM duration, glycated hemoglobin	NS: lens status, VA, CMT, IOP	6	3
Wang[5], 2010	RCT	China	[1](8) [2](8)	0	[1]57 (40-72) [2]59 (48-67)	NR	NS: VA, CMT, IOP	6	2
Gillies[15], 2011	RCT	Australia	[1]26(42) [2]28(42)	[1]1(1) [2]2(2)	[1]65.4±9.5 (15/11) [2]66.9±8.9 (15/13)	NS: DM duration, systematic hypertension, glycated hemoglobin	NS: lens status, VA, CMT, IOP	24	7

VA: Visual acuity; CMT: Central macular edema; DM: Diabetes mellitus; RCT: Randomized controlled trials; IOP: Intraocular pressure; NR: Not reported; NS: Not significant. [1]MLP with intravitreal triamcinolone acetonide pretreatment; [2]MLP alone group.

Table 2 Characteristics of laser procedures of trials included in the Meta-analysis

Trials (first author, year)	Type of DME	Dosage of IVTA	Time prior to MLP	Type of MLP	Parameters of MLP	Operators
Avitabile[12], 2005	Diffuse	4 mg (0.1 mL)	3mo	Grid	0.2-0.5s exposure time	NR
Lam[13], 2007	Diffuse	4 mg (0.1 mL)	1-2mo	Grid	50-200 μm light intensity, 0.1s exposure time	NR
Lee[14], 2009	Diffuse	4 mg (0.1 mL)	NR	Grid	50-200 μm light intensity, 0.1-0.2s exposure time	NR
Wang[5], 2010	Diffuse	4 mg (0.1 mL)	1wk	Grid	NR	NR
Gillies[15], 2011	Focal or diffuse	4 mg (0.1 mL)	6wk	Focal or grid	NR	NR

DME: Diabetic macular edema; IVTA: Intravitreal triamcinolone acetonide; MLP: Macular laser photocoagulation; NR: Not reported.

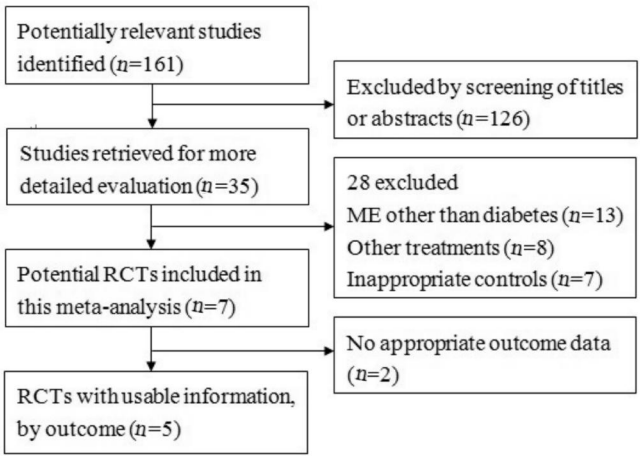

Figure 1 Flow diagram of literatures screening.

the adverse events, and three studies involved BCVA in logMAR units [12-14]. The present Meta-analysis involved 131 eyes receiving MLP with IVTA pretreatment and 133 eyes treated with MLP alone. The quality of each included study was roughly assessed according to the modified Jadad scale, and three trials had Jadad scores of 5 or more and two trials had Jadad scores of 3 or less. The main characteristics of the included studies were summarized in Table 1. In two studies, exact age and gender information were not reported but the authors declared that there were no statistical differences of age and gender ratio between the two groups. The main characteristics of the laser procedures of the included studies were listed in Table 2.

Best –corrected Visual Acuity As a functional outcome measure, BCVA was the most important criterion for evaluating efficacy. In three of the studies, BCVA was reported as a mean change in logMAR units, and measured by logMAR scale from baseline to follow-up months. There was evidence of statistical heterogeneity among studies at one-month follow up (P=0.01, I^2=77%), and a random-effect model was used. Pooling the results revealed that MLP with IVTA pretreatment significantly improved BCVA compared with MLP alone (control group) (WMD=-0.19, 95%CI: -0.36 to -0.02, P=0.03). At three- and six- month follow up, the IVTA pretreatment group showed a beneficial trend towards improvements of BCVA despite a lack of statistical significance (WMD=-0.15, 95%CI:-0.30 to 0.01, P=0.06; WMD=-0.10, 95% CI:-0.25 to 0.05, P=0.20, respectively). Similarly, there was evidence of statistical heterogeneity among studies (P=0.02, I^2=74%; P=0.03, I^2=72%, respectively). Again, a random-effect model was used (Figure 2).

Central Macular Thickness CMT represents the anatomic change and is considered a strong prognostic measure for levels of macular edema, so it was also assessed in this Meta-analysis. In all of the studies, CMT was reported as the mean change from baseline to follow-up months and was measured by OCT. There was also statistical heterogeneity among studies at one-month follow up(P<0.00001, I^2=95%), and a random-effect model was used. The pooled results revealed that the IVTA pretreatment group significantly reduced CMT compared with the control group (WMD=-159.88, 95%CI:-263.21 to -56.56, P=0.002). Similar efficacy was also found at three-month (WMD=-114.35, 95%

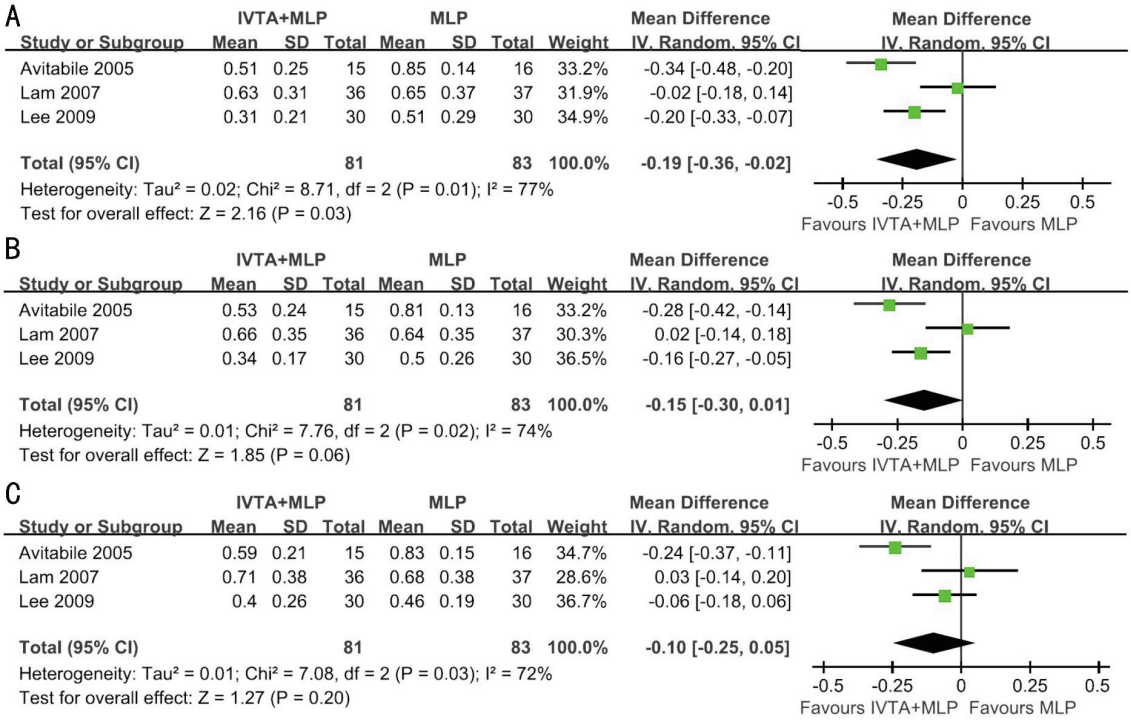

Figure 2 Forest plots showing mean difference in BCVA (logMAR) along with the associated 95% CI in the IVTA pretreatment group versus MLP alone group A: BCVA at 1mo; B: BCVA at 3mo; C: BCVA at 6mo.

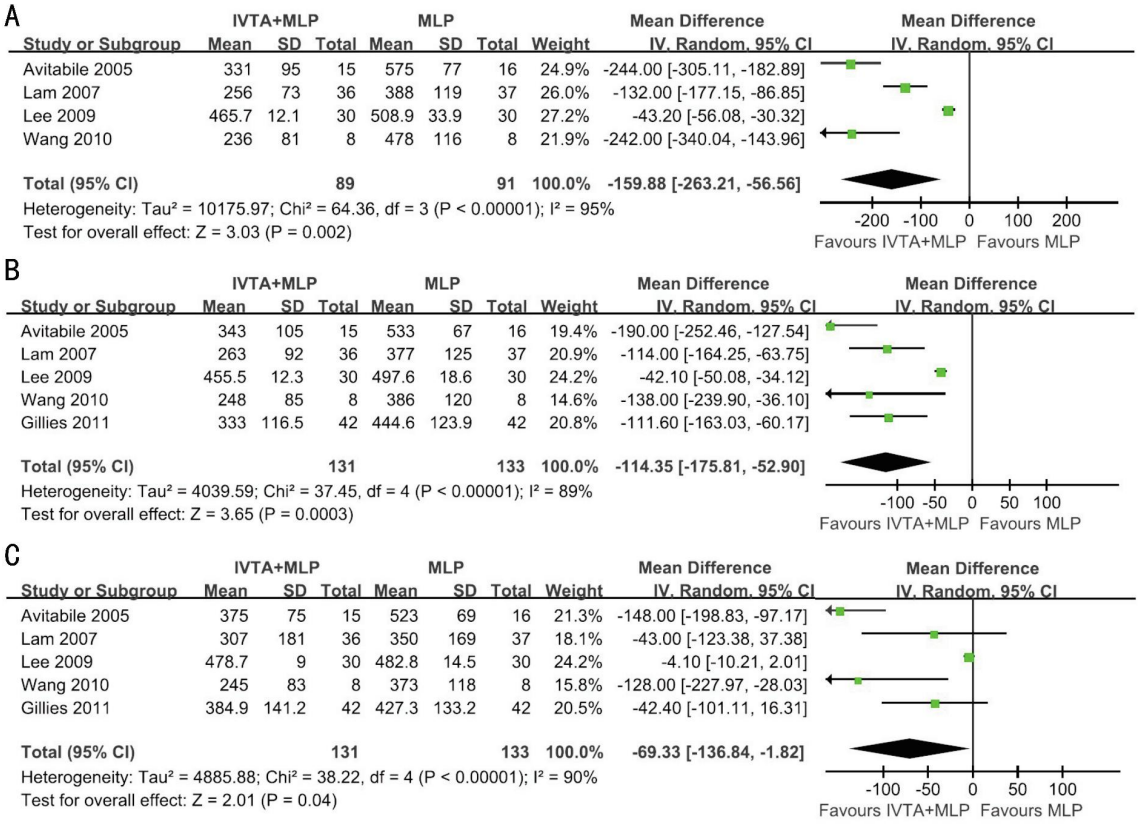

Figure 3 Forest plots showing mean difference in CMT along with the associated 95% CI in the IVTA pretreatment group versus MLP alone group A:CMT at 1mo; B: CMT at 3mo; C: CMT at 6mo.

CI:-175.81 to -52.90, P=0.0003) and six-month follow up (WMD=-69.33, 95%CI:-136.84 to -1.82, P=0.04). Similarly, there was evidence of statistical heterogeneity among studies (P<0.00001, I^2=89%; P<0.00001, I^2=90%, respectively). Again, a random-effect model was used (Figure 3).

Adverse Events All the studies reported data for elevation of intraocular pressure (IOP) during six-month follow up. Analysis of these data showed no evidence of statistical heterogeneity among studies (P=0.66, I^2=0%), and a fixed-effect model was used. The pooled results revealed that the

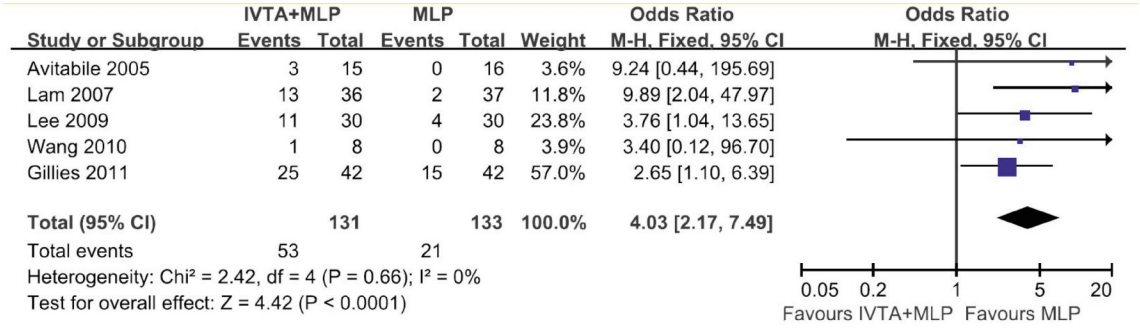

Figure 4 Forest plots showing mean difference in intraocular hypertension along with the associated 95% CI in the IVTA pretreatment group versus MLP alone group.

relatively higher rates of elevation of IOP (≥21 mm Hg) were observed in the IVTA pretreatment group compared with the control group (WMD=4.03, 95%CI: 2.17 to 7.49, P<0.0001, respectively) (Figure 4). However, all cases with IOP rise after injection could be managed with glaucoma medications. No other potential injection-related complications, such as endophthalmitis, retinal detachment and vitreous hemorrhage, were reported in the two groups.

Sensitivity Analysis Sensitivity analysis was independently performed by excluding the studies with low scores, and the exclusion of these studies did not change the results.

Publication Bias Based on funnel plots for the analysis of visual acuity, no obvious evidence of publication bias was found for the treatment outcome estimates (BCVA and CMT at six months after initial treatment) (Figures 5, 6). Since, however, the number of enrolled studies was small, we additionally applied the Egger method and Begg method to measure a publication bias. Both methods did not reveal a significant publication bias (BCVA at six months after initial treatment, Egger method: P=0.068, Begg method: P=0.296; CMT at six months after initial treatment, Egger method: P=0.056, Begg method: P=0.221).

DISCUSSION

In the studies by Wang *et al*[5], Lee *et al*[14] and Lam *et al*[13], the response to MLP combined with pretreatment of IVTA injection showed superiority compared with MLP-alone treatment for DME. However, the conclusions of Avitabile *et al*[12] and Gillies *et al*[15] were not in accordance. Which treatment is more effective remains controversial. Thus, we conducted this Meta-analysis to compare the efficacy of MLP combined with pretreatment of IVTA injection with MLP-alone treatment in patients with DME.

In our Meta-analysis, we found that the group received MLP with IVTA pretreatment had statistically significant improvements in visual acuity and CMT over the MLP-alone treatment group during the earlier follow-up period (1mo). At later visit (3 and 6mo), the IVTA-pretreated eyes continued to sustain a significant decrease in CMT after MLP while no significant improvements in visual acuity was observed when

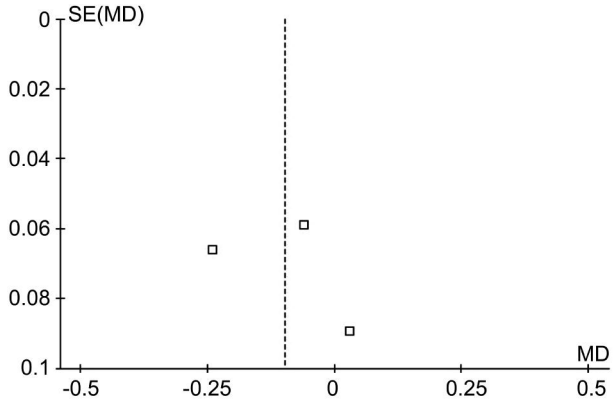

Figure 5 Funnel plots with respect to BCVA at 6mo follow up
SE: Standard error; MD: Mean deviation.

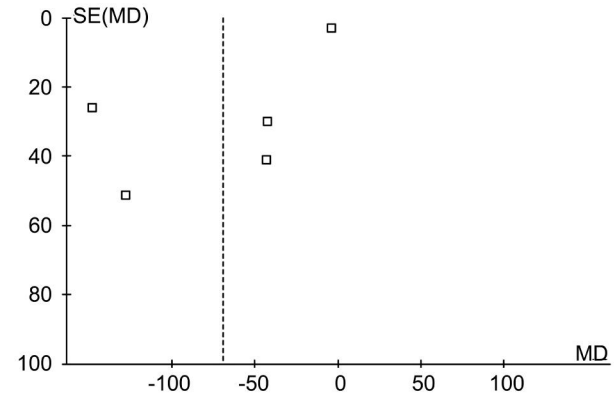

Figure 6 Funnel plots with respect to CMT at 6mo follow up
SE: Standard error; MD: Mean deviation.

compared with MLP-alone treatment. These results showed that there was no absolute correlation between anatomic change (CMT) and functional change (visual acuity). This relation between CMT and visual acuity in DME was discussed by previous studies, which reported a subset of eyes that showed paradoxical increases in CMT with increases in visual acuity or paradoxical decreases in CMT with decreases in visual acuity[16-17]. In addition, Browning *et al*[17] pointed out that not only CMT, but age, hemoglobin A_1C, and severity of fluorescein leakage in the center and inner subfields were responsible for the change in visual acuity. In another study conducted by Jonas *et al*[18], they concluded the varying degree of macular ischemia may

explain why some patients do not show a marked improvement in visual acuity despite a regression of the thickness.

As is well know, new vessel formation stimulated by vascular endothelial growth factor (VEGF) is the major pathology underlying diabetic maculopathy. Triamcinolone acetonide is usually used to treat macular edema in the clinical treatment, and has been shown to be efficacious in the reduction of CMT caused by macular edema. Furthermore, studies have suggested that IVTA injection is clinically effective in blocking the metabolic pathway of VEGF, and in anti-inflammatory, edematous, neovascular, and proliferative disorders [19-20]. However, one of the limitations is that the effects of IVTA injection are usually transient due to gradual drug absorption from the vitreous cavity. For patients presenting with DME for the first time, macular photocoagulation is currently recommended as an effective method to prevent neovascularization and progression of DME, but aggravation of macular edema with a decrease in visual acuity can occur in diabetic maculopathy after photocoagulation. However, for the reasons mentioned, MLP may not be the ideal treatment. There has thus been an initiative to study the effect of MLP with IVTA pretreatment on DME in patients.

A previous Meta-analysis reported that there was no significant difference in improving visual acuity except significant reduction of CMT when steroids injection combined with MLP was compared with MLP-alone treatment [21]. The previous Meta-analysis only evaluated two RCTs[12-13] with 51 eyes involving intravitreal steroid injection and which were already included in our Meta-analysis. However, two more RCTs were included in our Meta-analysis for a total of 264 eyes. From these results, our Meta-analysis for all logMAR scales of BCVA revealed that MLP with IVTA pretreatment could improve visual acuity for patients with DME during an earlier follow-up period (1mo). Moreover, CMT is an important criterion for evaluating macular edema and was assessed during follow-up periods. We revealed that MLP with IVTA pretreatment could reduce CMT in patients with DME. The results of our Meta-analysis were consistent with those of another previous Meta-analysis [22] comparing IVTA injection combined with panretinal photocoagulation (PRP) and macular photocoagulation (MPC) with PRP and MPC treatment for coexisting proliferative diabetic retinopathy and DME. And this former Meta-analysis showed statistically significant improvements in visual acuity and CMT with the treatment of IVTA injection combined with PRP and MPC. The reason for the efficacy of IVTA is that it reduces inflammation and changes retinal blood flow associated with photo-oxidative reactions induced by laser-tissue interactions [23]. Wilson *et al* [24] reported that an intravitreal injection of steroids in an animal (rabbit) model reduced the blood retinal barrier breakdown induced by retinal photocoagulation.

The emerging popularity of ocular steroids is also raising concerns about safety with use of these agents. Triamcinolone acetonide, one of ocular steroids, has several intravitreal injection-related complications, including increases in IOP, cataract formation, retinal detachment, vitreous hemorrhage and endophthalmitis with the elevation of IOP reported as one of the most common complication[19,25] Jonas *et al* [26] have reported that in 52% of patients treated with a 25 mg intraocular injection, IOP was elevated by more than 21 mm Hg. Wingate and Beaumont[27] have reported that after a 4 mg intraocular injection, within 3mo IOP was elevated by more than 5 mm Hg in 30% of the patients. Nevertheless, IOP of all patients was well controlled with glaucoma eye drops, and normalized 6mo after treatment without additional treatments required. Our Meta-analysis showed similar results to the abovementioned studies where during the follow-up period, the elevation of intraocular pressure (≥21 mm Hg) more occurred in eyes pretreated with IVTA injection than these cases treated with MLP alone. However, all patients were successfully controlled by glaucoma eye drop medication without surgery. Although no other visually significant injection-related side effects, including endophthalmitis, retinal detachment or vitreous hemorrhage, were encountered in our Meta-analysis, further investigation to assess the safety of the drug is needed.

Obviously, Meta-analysis has advantages compared with individual studies; however, some potential limitations in our study should be taken into account. The main limitation was that the number of studies which fulfilled the inclusion criteria of this Meta-analysis and which were eventually included into the analysis was relatively low as was the number of study participants. This led to a relatively low number of patient months in the Meta-analysis. In addition, some studies provided only crude-unadjusted data, which was probably the point of the high heterogeneity. Regression or stratification of study results could not be used to explore factors that could explain heterogeneities based on sample size or varying baseline levels. Another limitation of this Meta-analysis was the lack of standardization of laser timing after IVTA injection in the combined group and that the time interval between IVTA injection and MLP differed between studies. A recent study [28] showed that CMT decreases 1wk after IVTA injection and remains stable for 12wk or less. However, we believe that these differences between the included studies do not explain the conflicting evidence on pretreatment with IVTA on visual acuity. Even with the limitations, we feel the results of this Meta-analysis are clinically useful and can offer some valuable, preliminary data for treatment considerations.

Taken together, the results of the present Meta-analysis suggest that pretreatment of eyes with DME with IVTA before laser treatment may have a better anatomic outcome reflected by reduction in mean CMT during the follow-up

periods and significant improvements on visual acuity at the earlier follow-up point (1mo). At other time, the combined therapy shows a beneficial trend towards vision improvements but there is no statistical significance. Further studies, perhaps in the form of multi-center randomized controlled trials, could help elucidate the long-term effects of the two different treatment modalities in treating DME.

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REFERENCES

1 Liu XD, Zhou XD, Wang Z, Shen HJ. Comparison of intravitreal bevacizumab with macular photocoagulation for treatment of diabetic macular edema: a systemic review and Meta-analysis. *Int J Ophthalmol* 2014;7(6):1048-1055.

2 Qi HP, Bi S, Wei SQ, Cui H, Zhao JB. Intravitreal versus subtenon triamcinolone acetonide injection for diabetic macular edema: a systematic review and meta-analysis. *Curr Eye Res* 2012;37:1136-1147.

3 Cho HY, Kang SW, Kim YT, Chung SE, Lee SW. A three-year follow-up of intravitreal triamcinolone acetonide injection and macular laser photocoagulation for diffuse diabetic macular edema. *Korean J Ophthalmol* 2012;26(5):362-368.

4 Diabetic Retinopathy Clinical Research Network, Googe J, Brucker AJ, Bressler NM, Qin H, Aiello LP, Antoszyk A, Beck RW, Bressler SB, Ferris FL, Glassman AR, Marcus D, Stockdale CR. Randomized trial evaluating short-term effects of intravitreal ranibizumab or triamcinolone acetonide on macular edema after focal/grid laser for diabetic macular edema in eyes also receiving panretinal photocoagulation. *Retina* 2011;31(6):1009-1027.

5 Wang Y, Shi A, Shi X, Liu W. Clinical observation on treating diabetic macular edema with intravitreal triamcinolone acetonide and laser. *Yan Ke Xue Bao* 2010;25(1):22-25.

6 Mirshahi A, Shenazandi H, Lashay A, Faghihi H, Alimahmoudi A, Dianat S. Intravitreal triamcinolone as an adjunct to standard laser therapy in coexisting high-risk proliferative diabetic retinopathy and clinically significant macular edema. *Retina* 2010;30(2):254-259.

7 Maia OO, Takahashi BS, Costa RA, Scott IU, Takahashi WY. Combined laser and intravitreal triamcinolone for proliferative diabetic retinopathy and macular edema: one-year results of a randomized clinical trial. *Am J Ophthalmol* 2009;147(2):291-297.e2.

8 Aydin E, Demir HD, Yardim H, Erkorkmaz U. Efficacy of intravitreal triamcinolone after or concomitant with laser photocoagulation in nonproliferative diabetic retinopathy with macular edema. *Eur J Ophthalmol* 2009;19(4):630-637.

9 Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17(1):1-12.

10 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50(4):1088-1101.

11 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315(7109): 629-634.

12 Avitabile T, Longo A, Reibaldi A. Intravitreal triamcinolone compared with macular laser grid photocoagulation for the treatment of cystoid macular edema. *Am J Ophthalmol* 2005;140(4):695-702.

13 Lam DS, Chan CK, Mohamed S, Lai TY, Lee VY, Liu DT, Li KK, Li PS, Shanmugam MP. Intravitreal triamcinolone plus sequential grid laser versus triamcinolone or laser alone for treating diabetic macular edema: six-month outcomes. *Ophthalmology* 2007;114(12):2162-2167.

14 Lee HY, Lee SY, Park JS. Comparison of photocoagulation with combined intravitreal triamcinolone for diabetic macular edema. *Korean J Ophthalmol* 2009;23(3):153-158.

15 Gillies MC, McAllister IL, Zhu M, Wong W, Louis D, Arnold JJ, Wong TY. Intravitreal triamcinolone prior to laser treatment of diabetic macular edema: 24-month results of a randomized controlled trial. *Ophthalmology* 2011;118(5):866-872.

16 Larsson J, Zhu M, Sutter F, Gillies MC. Relation between reduction of foveal thickness and visual acuity in diabetic macular edema treated with intravitreal triamcinolone. *Am J Ophthalmol* 2005;139(5):802-806.

17 Diabetic Retinopathy Clinical Research Network, Browning DJ, Glassman AR, Aiello LP, Beck RW, Brown DM, Fong DS, Bressler NM, Danis RP, Kinyoun JL, Nguyen QD, Bhavsar AR, Gottlieb J, Pieramici DJ, Rauser ME, Apte RS, Lim JI, Miskala PH. Relationship between optical coherence tomography-measured central retinal thickness and visual acuity in diabetic macular edema. *Ophthalmology* 2007;114(3):525-536.

18 Jonas JB, Martus P, Degenring RF, Kreissig I, Akkoyun I. Predictive factors for visual acuity after intravitreal triamcinolone treatment for diabetic macular edema. *Arch Ophthalmol* 2005;123(10):1338-1343.

19 Al Dhibi HA, Arevalo JF. Clinical trials on corticosteroids for diabetic macular edema. *World J Diabetes* 2013;4(6):295-302.

20 Al Rashaed S, Arevalo JF. Combined therapy for diabetic macular edema. *Middle East Afr J Ophthalmol* 2013;20(4):315-320.

21 Steijns D, Duijvesz D, Breedijk MA, van der Heijden GJ. Steroid injection in addition to macular laser grid photocoagulation in diabetic macular oedema: a systematic review. *Acta Ophthalmol* 2010;88 (4): 389-393.

22 Liu L, Wu X, Geng J, Yuan Z, Chen L. IVTA as adjunctive treatment to PRP and MPC for PDR and macular edema: a meta-analysis. *PLoS One* 2012;7(9):e44683.

23 Nonaka A, Kiryu J, Tsujikawa A, Yamashiro K, Nishijima K, Kamizuru H, Ieki Y, Miyamoto K, Nishiwaki H, Honda Y, Ogura Y. Inflammatory response after scatter laser photocoagulation in nonphotocoagulated retina. *Invest Ophthalmol Vis Sci* 2002;43(4):1204-1209.

24 Wilson CA, Berkowitz BA, Sato Y, Ando N, Handa JT, de Juan E. Treatment with intravitreal steroid reduces blood-retinal barrier breakdown due to retinal photocoagulation. *Arch Ophthalmol* 1992;110(8):1155-1159.

25 Mikosz CA, Smith RM, Kim M, Tyson C, Lee EH, Adams E, Straif-Bourgeois S, Sowadsky R, Arroyo S, Grant-Greene Y, Duran J, Vasquez Y, Robinson BF, Harris JR, Lockhart SR, Török TJ, Mascola L, Park BJ; Fungal Endophthalmitis Outbreak Response Team. Fungal endophthalmitis associated with compounded products. *Emerg Infect Dis* 2014;20(2):248-256.

26 Jonas JB, Kreissig I, Sofker A, Degenring RF. Intravitreal injection of triamcinolone for diffuse diabetic macular edema. *Arch Ophthalmol* 2003; 121(1):57-61.

27 Wingate RJ, Beaumont PE. Intravitreal triamcinolone and elevated intraocular pressure. *Aust N Z J Ophthalmol* 1999;27(6):431-432.

28 Shimura M, Nakazawa T, Yasuda K, Shiono T, Iida T, Sakamoto T, Nishida K. Comparative therapy evaluation of intravitreal bevacizumab and triamcinolone acetonide on persistent diffuse diabetic macular edema. *Am J Ophthalmol* 2008;145(5):854-861.