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Comparison of intravitreal bevacizumab with macular photocoagulation for treatment of diabetic macular edema: a systemic review and Meta-analysis

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Abstract

• AIM: To further evaluate the efficacy and safety of intravitreal bevacizumab (IVB) versus macular photocoagulation (MPC) in treatment of diabetic macular edema (DME) by Meta-analysis.

• METHODS: Pertinent publications were identified through systemic searches of PubMed, Medline, EMBASE, and the Cochrane Controlled Trials Register up to 30 November, 2013. Changes in central macular thickness (CMT) in μm and best-corrected visual acuity (BCVA) in logMAR equivalents were extracted at 1, 3, 6, 12 and 24mo after initial treatment, and a Meta-analysis was carried out to compare results between groups receiving IVB and MPC.

• RESULTS: Five randomized controlled trial (RCTs) and one high-quality comparative study were identified and included. Our Meta-analysis revealed that both IVB and MPC resulted in the improvements of CMT and BCVA in eyes with DME at 1mo after initial treatment, with IVB being significantly superior to MPC (P=0.01 and 0.02, respectively). The improvements of both measure outcomes at 3, 6, 12 and 24mo after treatment did not vary significantly between the IVB groups and MPC groups (CMT at 3mo, P=0.85; at 6mo, P=0.29; at 12mo, P=0.56; at 24mo, P=0.71; BCVA at 3mo, P=0.31; at 6mo, P=0.30; at 12mo, P=0.23; at 24mo, P=0.52). However, the number of observed adverse events was low in all studies.

• CONCLUSION: Current evidence shows IVB treatment trends to be more effective in improvements of macular edema and vision in eyes with DME at an earlier follow up (1mo) compared with MPC. At other time, both interventions have comparable efficacy without statistical significances.

• **KEYWORDS:** intravitreal injection; bevacizumab; photocoagulation; diabetic macular edema; Meta-analysis

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INTRODUCTION

Diabetic macular edema (DME), a frequent manifestation of diabetic retinopathy, is the foremost cause of central vision loss in diabetic patients, and the worldwide prevalence of diabetes is estimated to rise to 366 millions in 2030[1]. The 10y incidence of macular edema in patients with type 2 diabetes was up to 14%, and 29% of type 1 progressed into DME over a 25y period [2,3]. If left untreated, 20% to 30% of patients with DME will experience a doubling of the visual angle within 3y[2]. Hence, to find safe and effective treatment of DME becomes urgent.

The pathogenesis of DME is multifactorial. However, it has been suggested that DME is predominantly caused by inflammatory factors and excessive vascular permeability resulting in the leakage of fluid and plasma constituents, such as lipoproteins into the retinal layers, leading to thickening of the retina. Macular photocoagulation (MPC) was proved to be useful in decreasing macular thickness and limiting vision loss in the past three decades and still remains the standard-of-care treatment for DME. In the Early Treatment Diabetic Retinopathy Study (ETDRS), laser photocoagulation of eyes with clinically significant macular edema reduced the risk of moderate visual loss by approximately 50%[4]. In spite of treatment, unsatisfactory outcomes are frequent, and 12% treated eyes developed moderate visual loss. Furthermore, this treatment can be destructive and its adverse effects in addition to the suboptimal efficacy have led to the advent of potential new therapies in the management of DME[5].

Recently, pharmacotherapy, such as intravitreal injection of biological response modifiers that block vascular endothelial growth factor (VEGF), has been developed to increase the efficacy of controlling macular edema and achieving better visual prognosis [6-8]. In diabetic eyes, the up-regulation of

VEGF has currently been deemed to be associated with the breakdown of the blood-retinal barrier and an increase in retinal vessel permeability resulting in macular edema [9-11]. Bevacizumab is a full-length recombinant humanized monoclonal antibody that blocks all forms of VEGF, and commonly used as an off-label therapeutic option in treating DME. Furthermore, intravitreal bevacizumab (IVB) injection has been reported to be effective in reducing macular edema and improving the best-corrected visual acuity (BCVA)[12-14]. Although not currently approved by the US Food and Drug Administration for intraocular use, the infusion of 1.25-2.5 mg of bevacizumab into the vitreous cavity has been performed without significant intraocular toxicity [15]. Therefore, it is of interest to uncover which treatment modality is more effective and safe for DME. The purpose of this Meta-analysis is to further evaluate the effect of IVB in comparison to standard macular laser photocoagulation in management of DME. Additionally, we report the adverse events described with these two therapies.

MARERIALS AND METHODS

Literature and Search Strategy Two experienced investigators independently searched the following electronic databases: PubMed, Medline, EMBASE, and the Cochrane Controlled Trials Register up to 30 November, 2013. There were no language or date restrictions on the publications. The search strategy was based on the combination of medical subject heading and free text word. Search terms used were "bevacizumab", "avastin", "laser", "photocoagulation" and "DEM". When titles and/or abstracts met the objectives, the full article would be retrieved. The reference lists of every primary article and previous systematic review were scrutinized for information about any additional citations. Additional information from the Internet search engines, such as Google and Yahoo, was also incorporated.

Inclusion Criteria and Data Extraction Studies were considered for inclusion if they met the following criteria: 1) randomized controlled trials (RCTs) or high-quality comparative studies; 2) interventional therapies for DME consisting of IVB versus MPC; and 3) all articles containing sufficient information, where pre- and post-treatment macular thickness and visual acuity were measured and recorded as mean ±SD. Exclusion criteria were: 1) studies of macular edema secondary to causes other than diabetic retinopathy (DR); and 2) studies that focused on combined therapies. For duplicated publications, only the data from the longest period of follow-up were used in the analysis. All studies were screened for quality and relevance. The quality of RCTs was assessed using the Jadad scale (with a score range of 0-5), and comparative multicenter study had to meet the criteria of the case, matched by the patient's characteristics [16]. In addition, studies had to have well-defined patient inclusion criteria. For each study, the following data were extracted:

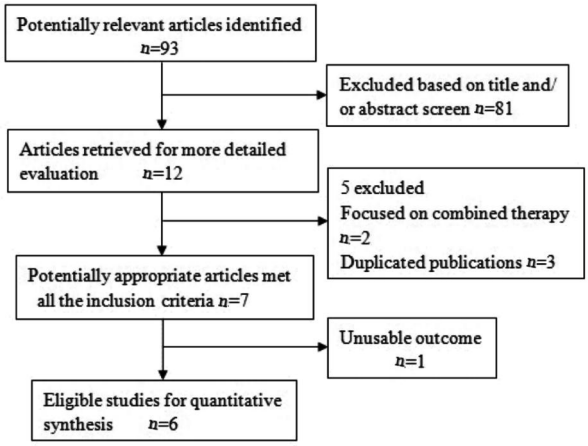

Figure 1 Flow diagram of literature retrieval.

name of first author and year of publication; geographical location of study; study design; sample size; gender and mean age of the participants; treatment method; duration and completeness of follow-up; and treatment outcome in terms of CMT and BCVA. The corresponding authors of the individual trials were also contacted for unpublished information. Data extraction was conducted according to the predesigned data extraction form by the two investigators independently, and discordance was resolved through discussion until 100% agreement was reached.

Statistical Analysis A Meta-analysis on the effect of IVB or MPC on DME was performed with Cochrane Review Manager (RevMan; version5.0 software) using 2-tailed P values and a 95% confidence interval (CI). The treatment effect was estimated by means of weighted mean deviation (WMD) in CMT in μm and BCVA in logMAR equivalents. Heterogeneity was assessed using the Chi-square test on Cochrane's Q statistic and by calculating I^2. We used a fixed-effect model in the Meta-analysis if there was no statistical heterogeneity ($P>0.1$, $I^2<50\%$). However, a random-effect model was applied when there was statistical heterogeneity ($P\leqslant 0.1$, $I^2\geqslant 50\%$). A sensitivity analysis was performed by excluding the non-randomized studies. The funnel plots, Begg's rank correlation test[17] and Egger's linear regression test [18] were introduced to assess the publication biases, with $P<0.1$ indicating potential bias.

RESULTS

Characteristics of the Studies The selection process for inclusion of reports is outlined in Figure 1. A total of 93 articles that were potentially relevant were yielded by computerized literature searches, and 7 of which met all of the predefined inclusion criteria. Then, a full review was further performed for the remaining 7 articles, and one was further excluded because its data could not be pooled in any comparison. Ultimately, five RCTs [19-23] and one high-quality comparative study[24] published between 2008 and 2013 were included into the Meta-analysis, which included a total of 563 participants with 610 eyes.

Table 1 Main characteristics of studies included in this Meta-analysis

Trials (first author, a)	Trial design	Region	Major inclusion criteria	No. of eyes	Mean age (M/F)	System baselines	Ocular baselines	Dosage of IVB (mean times)	Type of MPC	Duration (mo)	Jadad score
Faghihi, 2008	RCT	Iran	VA≤20/40 (ETDRS chart), CMT≥250 μm	[1]42 [2]47	[1]59±6 (23/19) [2]56±7 (22/25)	NS: DM duration, Systematic hypertension	NS: VA, CMT, IOP	1.25 mg (1)	Focal/grid	4	3
Solaiman, 2010	RCT	Egypt	CSME, CMT≥350 μm	[1]21 [2]19	[1]57 (11/10) [2]56 (11/8)	NS: DM duration	NS: Lens status, VA, CMT, IOP,	1.25 mg (1)	Grid	6	2
Azad, 2012	RCT	India	CSME, CMT≥250 μm	[1]20 [2]20	[1]53.6 (12/8) [2]56.4 (10/10)	NS: DM duration, HbA_{1c}, systematic hypertension	NS: Lens status, VA, CMT, IOP, previous laser	1.25 mg (2.7)	Grid	6	3
Rajendram, 2012	RCT	UK	Center-involving CSME, CMT≥270 μm, 35≤VA≤69 (ETDRS letters at 4 m)	[1]42 [2]38	[1]64.9±9.4 (30/12) [2]63.5±8.1 (25/13)	NS: DM duration, HbA_{1c}, systematic hypertension, ethnicity	NS: Lens status, VA, CMT, IOP, previous laser	1.25 mg (13)	Focal/grid	24	5
Soheilian, 2012	RCT	Iran	CSME, 20/300≤VA≤20/40 (ETDRS criteria)	[1]50 [2]50	[1]60.5±5.9 (23/27) [2]61.0±5.3 (28/22)	NS :DM duration, HbA_{1c}, systematic hypertension,	NS: Lens status, VA, CMT, IOP, DR	1.25 mg (3.1)	Focal/grid	24	5
Arevalo, 2013	Controlled, nonrandomized	Multi-center	Center-involving CSME, CMT≥250 μm	[1]141 [2]120	[1]59.4±10.8 (63/57) [2]64.3±9.0 (46/48)	NS: Glycemic control, HbA_{1c}, hypertension	NS: VA, CMT, IOP, DR, previous laser	1.25 mg (5.8)	Grid	24	-

IVB: Intravitreal bevacizumab; MPC: Macular photocoagulation; [1]IVB group; [2]MPC group; RCT: Randomized controlled trial; CSME: Clinically significant macular edema; M: Male; F: Female; DM: Diabetes mellitus; DR: Diabetic retinopathy; IOP: Intraocular pressure; NS: No significance; UK: United Kingdom; Multicenter: 5 centers from Venezuela, Costa Rica, Argentina, Spain, and Puerto Rico.

The detailed characteristics of the six included studies are described in Table 1. The sample sizes varied from 40 to 261 subjects, and durations of follow-up varied from 4 to 24mo. Both male and female participants were enrolled in almost equal proportion, and distribution of age and history of DME also did not vary significantly between the IVB groups and the MPC groups.

Central Macular Thickness CMT represented the anatomic change, and four studies [19,20,23,24] reported data on CMT at 1mo after the initial treatment. There was statistical heterogeneity among studies for this measure of effect (P< 0.0001, I^2=86%), and a random-effect model was used. Both interventions resulted in decreased CMT, and IVB was significantly more effective at 1mo compared with MPC (WMD=-48.13; 95% CI: -84.79 to -11.48; P=0.01). Four studies [19,20,23,24] reported data on CMT at 3mo after the initial treatment, and there was no statistical heterogeneity among studies (P=0.37, I^2=4%). A fixed-effect model was used, and changes in CMT did not vary significantly between the IVB and MPC groups (WMD=-1.36; 95% CI: -15.03 to 12.32; P= 0.85). Four studies [20-24] reported data on CMT at 6mo after the initial treatment, and showed statistical heterogeneity (P=0.04, I^2=65%). A random-effect model was used, and changes in CMT at 6mo after IVB treatment did not vary significantly as compared to those that received MPC (WMD=16.11; 95%CI: -13.90 to 46.12; P=0.29). Only three studies[22-24] expressed data on CMT at 12 and 24mo after the initial treatment, and showed no statistical heterogeneity (P=0.56 and 0.92, respectively, and both I^2= 0%). Again, changes in CMT at these two follow-up points after IVB treatment also did not vary significantly as compared to those that received MPC (WMD=-5.49; 95%CI: -24.05 to 13.08; P= 0.56 and WMD=3.24; 95% CI: -13.74 to 20.22; P=0.71, respectively; Figure 2).

Visual Acuity As functional outcome measure, BCVA was most important for evaluating efficacy. The BCVA was converted to logarithm of the minimum angle of resolution (logMAR) vision and was summarized by means of Meta-analysis. Figure 3 is a forest plot of BCVA results comparing IVB with MPC. Four studies [19,20,23,24] reported data on BCVA at 1mo after the initial treatment. There was statistical heterogeneity among studies for this measure of effect (P=0.005, I^2=77%), and a random-effect model was used. Both interventions resulted in the improvements of vision acuity, and IVB was significantly more effective at 1mo compared with MPC (WMD=-0.13; 95%CI: -0.25 to -0.02; P=0.02). Four[19,20,23,24], three[20,23,24], two[23,24] and two[23,24] studies reported data on BCVA at 3, 6, 12 and 24mo after the initial treatment, respectively, and demonstrated no statistical heterogeneity among trials at any of these follow-up periods (P=0.96, 0.79, 0.82 and 0.39, respectively, and all I^2=0%). A fixed-effect model was used, and the improvements in BCVA did not vary significant between the IVB and MPC groups at 3 (WMD=-0.03; 95%CI: -0.10 to 0.03; P=0.31), 6 (WMD=-0.04; 95% CI: -0.13 to 0.04; P =0.30), 12 (WMD=-0.05; 95% CI: -0.14 to 0.03; P =0.23) and 24mo (WMD=0.03; 95%CI: -0.06 to 0.12; P=0.52).

Adverse Effects Adequate data about complications occurring at different follow-up intervals could not be determined from the studies, thus limiting performance of a Meta-analysis to assess side-effects. Significant adverse effects reported in different studies in each treatment arm are presented in Table 2, and most of which were reported by Rajendram *et al* [22], including IOP rise in 5 eyes in the IVB group, and reduction of vision in 5 eyes and 4 eyes in the IVB group and MPC group respectively. A further systemic adverse effects, related to cardiovascular (2 myocardial infarctions, 1 angina, and 1 coronary artery bypass graft) and cerebrovascular accident (1 stroke), were reported by Rajendram *et al* [22] only. In the IVB group, there were 2 myocardial infarctions, 1 of which was fatal, and the other was described as minor with a full recovery. In the MPC group, there were one angina requiring hospital observation and one stroke.

Sensitivity Analysis Sensitivity analysis was performed by excluding the non-randomized study, and the exclusion of this study did not change the results.

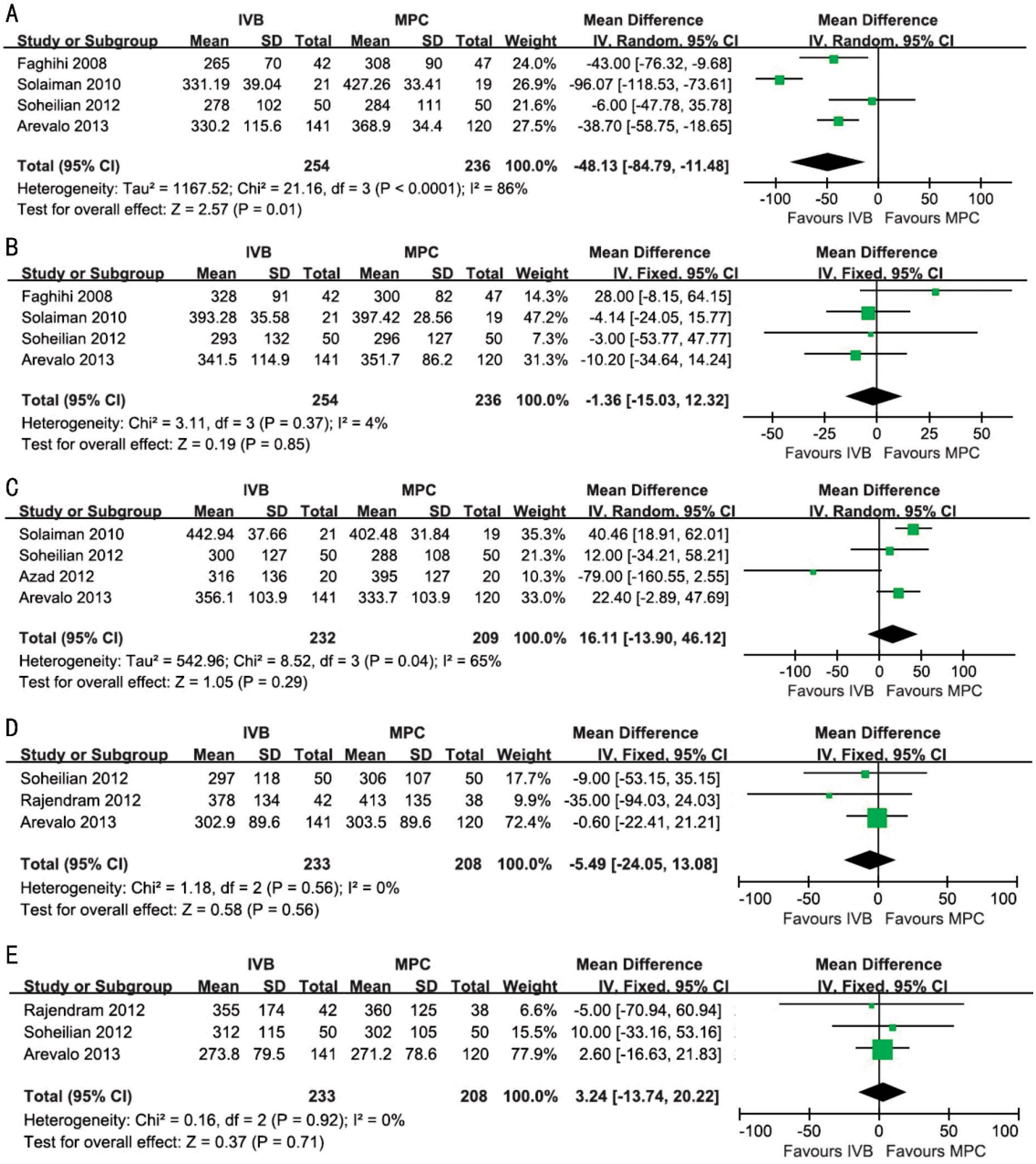

Figure 2 These forest plots show the mean differences in CMT (μm) along with associated 95% CIs, comparing IVB to MPC at 1mo (A), 3mo (B), 6mo (C), 12mo (D) and 24mo (E). Negative values in these plots favor IVB over MPC; positive values favor MPC over IVB.

Publication Bias Funnel plots for CMT and BCVA at one month follow-up were displayed. According to the funnel plots, the studies were within the confidential intervals and the shapes of the funnel plots did not reveal any evidence of obvious asymmetry (Figures 4, 5). However, the numbers of studies were small, so Begg's test and Egger's test were performed to further evaluate quantitatively the publication biases. According to the results, all the *P* values of Begg's test and Egger's test were above 0.1 (Table 3). Therefore, there was no strong evidence of publication bias and the results were reliable.

DISCUSSION

DME has been recognized as being the main cause of legal blindness in diabetes mellitus (DM). Extensive research has been underway for decades to understand the precise pathogenesis and potential treatment modalities to improve, stabilize, and prevent DME.

Laser photocoagulation has been the gold standard of treatment of DME, and its merits were proven by the ETDRS[5]. Ocular corticosteroids have also been used by vitreoretinal specialists to treat unresponsive cases but are often associated with well-recognized side-effects, such as cataract and glaucoma[25,26]. Despite these treatments, many patients do not respond and will continue to lose vision. As more studies have supported the role of VEGF in influencing structural and functional changes in diabetic retinopathy and macular edema, bevacizumab is increasingly being used as an off-label therapeutic option for DME.

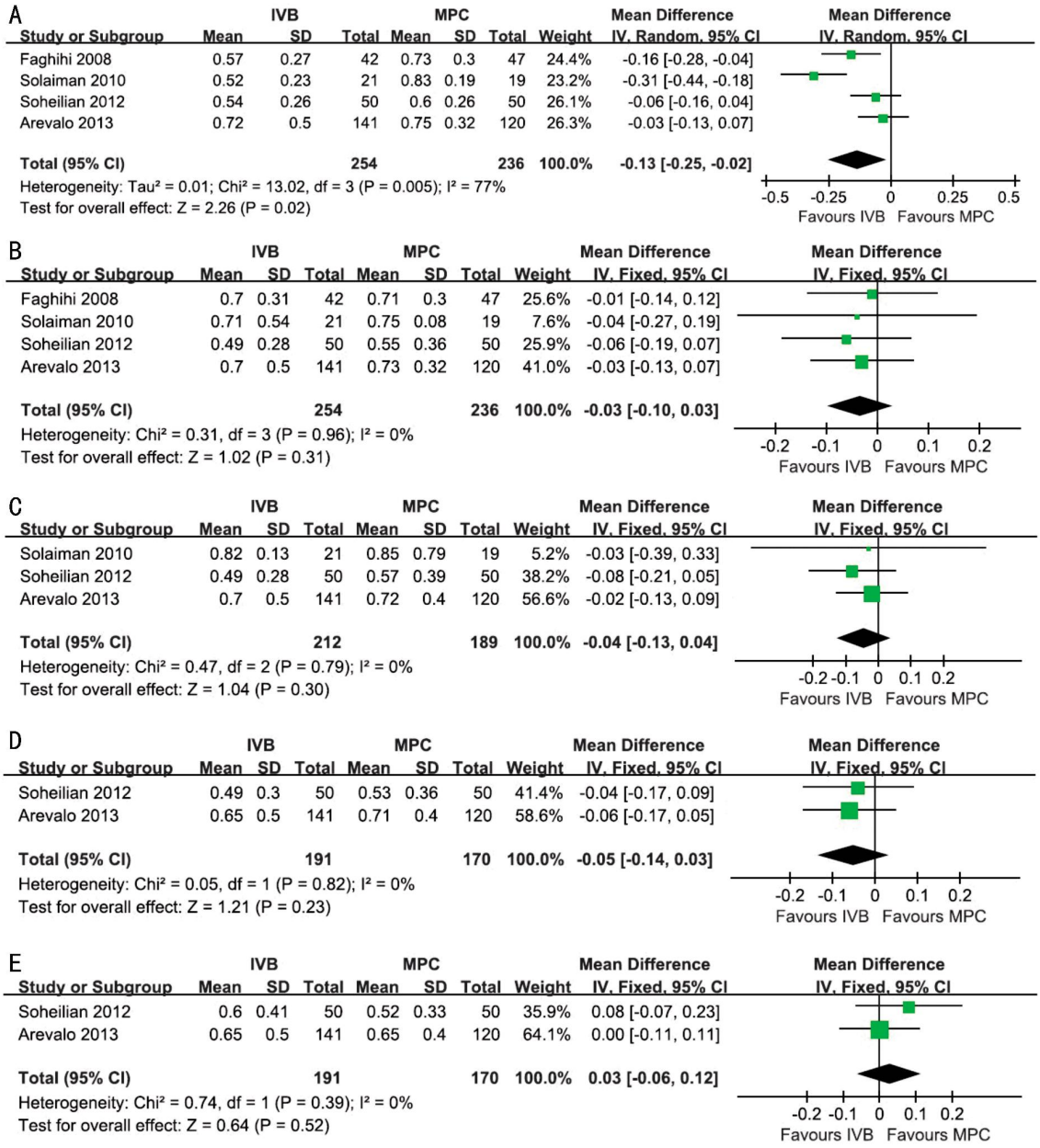

Figure 3 These forest plots show the mean differences in BCVA (log MAR) along with associated 95% CIs, comparing IVB to MPC at 1mo (A), 3mo (B), 6mo (C), 6mo (D), and 24mo (E). Negative values in these plots favor IVB over MPC; positive values favor MPC over IVB.

Table 2 Adverse effects reported in various trials

Study	Group	Progression of cataract	Progression of RT	Increase of IOP	Reduction of vision	Systemic events
Faghihi *et al*[19]	IVB	-	-	-	-	-
	MPC	-	-	-	-	-
Solaiman *et al*[20]	IVB	-	-	-	-	-
	MPC	-	-	-	2 eyes lost two lines	-
Azad *et al*[21]	IVB	4 eyes	-	-	-	-
	MPC	-	-	-	-	-
Rajendram *et al*[22]	IVB	-	-	5 (4 transient) ⩾30 mm Hg	4 transient (>15 or <30 ETDRS letters), 1 (>30 letters)	2 MI, 1 coronary artery bypass graft
	MPC	-	-	-	1 transient and 3 at 24mo (>15 or <30 letters)	1 angina-hospital admission,1 stoke
Soheilian *et al*[23]	IVB	1 eye	7 eyes	-	-	-
	MPC	1 eye	6 eyes	-	-	-
Arevalo *et al*[24]	IVB	-	-	-	-	-
	MPC	-	-	-	-	-

RT: Retinopathy; MI: Myocardial infarction; IVB: Intravitreal bevacizumab; MPC: Macular photocoagulation; IOP: Intraocular pressure.

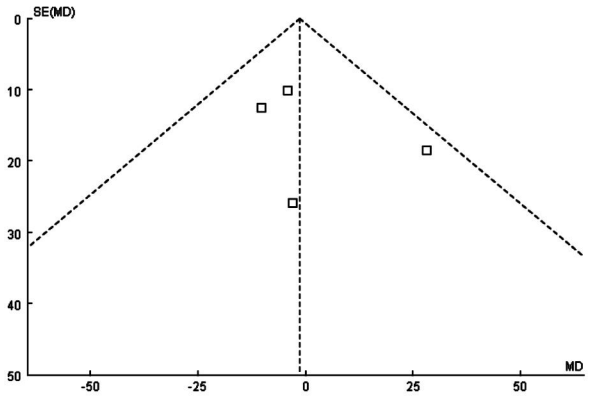

Figure 4 Funnel plots with respect to CMT at 1mo after initial treatment SE: Standard error; MD: Mean deviation.

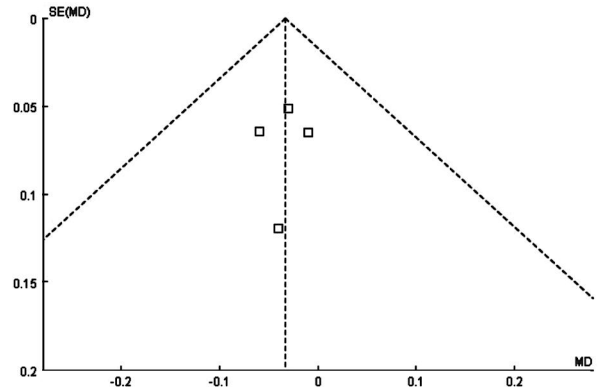

Figure 5 Funnel plots with respect to BCVA at 1mo after initial treatment.

Table 3 Outcomes of Begg's test and Egger's test

Parameters	Begg's test		Egger's test	
	Z	*P*	*t*	*P*
CMT	0.52	0.602	-1.2	0.352
BCVA	0.11	1.000	-0.28	0.793

CMT is a strong prognostic measure of DME levels. Intravitreal anti-VEGF drugs have been shown to be beneficial in reducing CMT and edema secondary to retinal vascular diseases, including diabetic retinopathy in short term[11,27]. And Haritoglou *et al*[28] reported a CMT reduction of 15%-25% with multiple bevacizumab intravitreal injections. Similarly, MPC has also been proved to be effective in reducing macular edema, and its beneficial effect is believed to be due to induction of proliferation of both the endothelial cells in retinal capillaries and the retinal pigment epithelial cells, thus improving the efficacy of both the inner and outer blood-retinal barriers[29]. We illustrated that use of either IVB or MPC resulted in critical reduction in CMT at different points post-treatment. And significant decrease in CMT was found in the IVB groups compared with the MPC groups at 1mo. This is likely due to the transient increase in macular edema after laser photocoagulation. However, CMT at other follow-up points indicated no superiority associated with MPC treatment in the meta-analysis. Additional studies are needed to further assess CMT changes in IVB and MPC interventions.

Vision acuity (VA), a primary measure of treatment efficacy, is an exceedingly important function outcome. The beneficial effect of anti-VEGF drugs or laser therapy on VA improvements in patients with DME has been demonstrated in a few recent published studies [7,9,11]. In the Meta-analysis, we found that both IVB and MPC treatments improve VA of DME eyes, with IVB being significantly superior to MPC at 1mo. However, the meaningful superiorities of IVB appear to wane over longer follow-up periods. The reason why the significant difference was not observed in VA at other follow-up points may be the limited effective time of bevacizumab, because its half-life in the eyes is only 9.8d[30]. Many studies have indicated that the effectiveness of IVB on VA was greater in patients with macular edema in an early follow-up period[31,32]. And pharmacokinetic data also suggest a single intravitreal injection of 1.25 mg bevacizumab is effective for 6-7wk [33]. Furthermore, the limitations of IVB include regression of visual acuity and an increase in the central macular thickness (CMT) within a few weeks after treatment [25], which meant that more frequent injections were needed. Although studies have reported that MPC had the ability to stabilize VA, it had no significant improving effect on VA in long term.

The emerging popularity of anti-VEGF agents is also raising concerns about safety with long-term use of these agents. Bevacizumab, as a pan-VEGF blocker, has the potential to inhibit important physiological functions of VEGF such as wound healing and development of collaterals deemed significant in myocardial or peripheral ischemia, thus potentially causing systemic adverse events [34]. However, recent studies have shown that bevacizumab treatment did not cause any detectable retinal damage, and appears to be safe and well-tolerated as long as 12mo follow up [35]. Furthermore, Michaelides *et al*[36] reported that both IVB and MPC were all safe and not significantly different in macular perfusion determined by fundus fluorescein angiography. Although a Meta-analysis for side effects of IVB or MPC was not performed in our study, the number of observed adverse events was low. Only Rajendram *et al*[22] reported IOP rise in the IVB group and cardio- or cerebro-vascular events in both groups. However, there were no cases of endophthalmitis, no unusual or previously unrecognized complications related to intravitreal injection, and no apparent increase in any variable used to assess retinal perifoveal capillary perfusion. While the incidences of these emerging complications were low, however, additional investigations are needed in the future.

Several limitations of the present meta-analysis could affect the final conclusion. First, the nonrandomized studies, as opposed to RCTs, were prone to bias due to uncontrolled confounding. Second, a total of only six studies were involved and all participant studies except the study by Arevalo *et al*[24] had a relatively small sample size. Third,

most 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. Fourth, we did not also assess the effect of the combination of MPC with anti-VEGF drugs, although studies have reported that such a combined therapy was one of the treatment options for the management of DME. In addition, many clinical investigations have demonstrated the efficacy of ranibizumab, another Food and Drug Administration-approved anti-VEGF drug for treatment of DME[37,38]. However, few studies comparing the efficacy of bevacizumab with ranibizumab for the treatment of DME could be found. Furthermore, considering medical expenses, bevacizumab appear to be more acceptable for the majority of DME patients, especially those in undeveloped countries.

As far as the authors are aware, this is the first study to consolidate and review current knowledge of published data regarding the use of bevacizumab versus MPC in DME, and despite the aforementioned limitations, the authors feel that the results of this Meta-analysis is clinically useful and can offer some valuable, preliminary data on this subject. Our data suggests that IVB yields better visual outcomes and achieves greater reduction in macular thickness in DME eyes compared with MPC during the early follow-up period. However, the current literature does not seem to provide sufficient evidence to show significant difference for their long-term efficacy when used IVB versus MPC to treat DME. Further studies, perhaps in the form of multi-center RCTs, could help elucidate the long-term effects of the two different treatment modalities in treating DME.

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Conflicts of Interest: Liu XD, None; **Zhou XD,** None; **Wang Z,** None; **Shen HJ,** None.

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