·**Informatics Research**·

Intravitreal triamcinolone versus intravitreal bevacizumab for diabetic macular edema: a meta-analysis

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Abstract

• **AIM: To compare the efficacy of the sole intravitreal triamcinolone (IVT) versus intravitreal bevacizumab (IVB) alone or IVB combined with IVT in the treatment of diabetic macular edema (DME).**

• **METHODS: Pertinent publications were identified through systematic searches of database and manually searching. Methodological quality of the literatures was valuated according to the Jadad Score. RevMan 5.1.0 was used to do the meta-analysis. Heterogeneity was determined and sensitivity was conducted.**

• **RESULTS: Six studies were ultimately included in the meta-analysis. The results of our analysis showed IVT had a statistically significant improvement in vision over the IVB at 1 month and 3 months ($P<0.01$). However, the reduction was not significant regarding central macular thickness (CMT) during the earlier (1 month and 3 months) follow-up period ($P=0.12$, $P=0.41$, respectively). At later visit (6 months), IVT had a significant decrease in CMT when compared to IVB ($P<0.01$) while no significant improvement in visual acuity (VA) was observed ($P=0.14$). The incidence of intraocular hypertension was 13/102 in IVT group during follow-up period while 0/103 in IVB group. The difference was significant ($P<0.01$). With regards to IVT versus IVB combined with IVT, there were no significant differences in CMT at 1 month ($P=0.86$) and 3 months ($P=0.06$). The incidence of intraocular hypertension was 6/67 in IVT group during follow-up period while 4/66 in IVB+IVT group. But the difference was not significant ($P=0.53$).**

• **CONCLUSION: Current evidence shows IVT is superior in improving VA at earlier follow-up (1 month and 3 months) and in reducing CMT at later follow-up (6 months) for DME. At other time, it is in favor of IVT treatment but there are no statistically significances. However, IVT has the side-effect of ocular hypertension. There is no adequate evidence of the benefit adding IVB to IVT in contrast to IVT alone.**

• **KEYWORDS:** triamcinolone; bevacizumab; diabetic macular edema; meta-analysis

INTRODUCTION

D iabetic macular edema (DME) is one of the most common causes of visual loss as a complication of diabetes in the working population[1]. Besides, the worldwide prevalence of diabetes is estimated to rise to 366 millions in 2030 [2]. The 10 years incidence of macular edema in patients with type 2 diabetes was 14% and 29% of type 1 developed DME over a 25-year period [3,4]. Hence, finding safe and effective treatment of DME becomes so important .

At present, there have been many therapies for the treatment of DME including laser photocoagulation, intravitreal injection of anti-vascular endothelial growth factor (VEGF) drug, ocular corticosteroids and pars plana vitrectomy. Laser photocoagulation was proved to be useful in limiting vision loss in the past three decades and is still considered a gold standard therapy for the treatment of diabetic retinopathy[5,6]. There is growing evidence that intravitreal available agents in combination with laser photocoagulation is more advantageous than laser alone in reducing maculae edema[7,8]. Base on our knowledge, intravitreal corticosteroids and anti-VEGF are being widely used as pharmacotherapy for DME. Ranibizumab and bevacizumab are two main anti-VEGF agents for DME. Although ranibizumab has been recently approved by the United States Food and Drug Administration for the treatment of DME, its cost is immense. Bevacizumab, which costs much less than ranibizumab, is commonly used as an off-label therapeutic option in treating DME. Many studies have indicated

intravitreal bevacizumab (IVB) was effective for reducing DME [9-14]. Triamcinolone, one of corticosteroids, has the effect of anti-inflammatory and anti-angiogenic. Many reports have demonstrated the usefulness of intravitreal triamcinolone (IVT) in patients with DME [15-18]. With the increasing use of IVB and IVT, it is of interest to confirm which agent is more effective and safe.

This meta-analysis was performed to compare the efficacy of the sole IVT versus IVB alone or IVB combined with IVT in patients with DME. The results could be important to choose the better drug as adjunctive treatment to laser photocoagulation and also help to clarify the pathogenesis of DME.

MATERIALS AND METHODS

We searched Medline, Embase, Web of science, and the Cochrane library from inception until January 2013. There were no language or date restrictions on the publications. The search strategy was based on combinations of medical subject headings and free text word. Search terms used were "diabetic macular edema", "bevacizumab", "avastin", "triamcinolone", "randomized controlled trials". The searches were supplemented by manually searching the bibliographies of included studies and reviews.

Inclusion and Exclusion Criteria Inclusions for analysis were restricted to: 1) Study design and intervention: randomized clinical controlled trials (RCCTs) which compared IVB of any dose with or without IVT of any dose versus IVT of any dose in the treatment of DME; 2) Population: trials that enrolled participants of any age and sex with any type of DME (focal or diffuse, primary or refractory); 3) Outcome measurement: studies that have indicated visual acuity (VA) and central macular thickness (CMT) were the main outcome measures and reported as mean ±SD. Exclusion criteria were: 1) Studies of macular edema secondary to causes other than diabetic retinopathy (DR); 2) Studies of DR without macular edema; 3) Studies that were not randomized controlled trials.

Data Extraction and Quality Assessment For each study, the following data were extracted: 1) General data: name of first author, the year of publication and location of the study, major inclusion criteria, various intervention groups, number of subjects, age and gender and duration of follow-up; 2) Outcomes: means and standard deviations (SDs) of final value after treatment in CMT and VA of logarithm of the minimum angle of resolution (logMAR) units, the number of cases which had IOP greater than 21mmHg. The methodological quality of the included trials were assessed using the Jadad scale [19]. Studies were scored according to three main study characteristics: randomization, blinding and participant withdrawals dropouts. A study was recognized as high quality if it had a Jadad score (with a score range of 0-5) of three points or greater.

Assessment of Risk of Bias The following parameters were assessed: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias) and other biases that included: an extreme baseline imbalance, risk of bias related to the specific study design used, trial stopped early due to some data-dependent process. For the above questions, a judgment of "Yes" of each parameter indicated low risk of bias, "No" indicated high risk of bias, and "unclear" indicated unclear or unknown risk of bias.

Statistical Analysis Statistical analysis was performed using the Review Manager 5.1.0 software from the Cochrane Collaboration. Continuous data were expressed as means and standard deviations, and weighted mean differences (WMD) were calculated while dichotomous data were calculated as relative risk (RR). Hence, the mean WMD (VA and CMT) and RR (IOP) between groups (IVT versus IVB or IVT versus IVT/IVB) were analyzed and provided a 95% confidence interval (CI). A Chi-square test and an I^2 test were used to test for statistical heterogeneity between trials. We used the fixed effects model in the meta-analysis if there was no statistical heterogeneit($P > 0.1$, $I^2 < 50\%$). However, when there was statistical heterogeneity($P \leqslant 0.1$, $I^2 \geqslant 50\%$), sources of heterogeneity should be examined to make sure if a random-effect model could be applied.

RESULTS

Results of Research Figure 1 shows a flow diagram depicting the selection process of articles. A total of 80 articles that were potentially relevant were identified through database searches, and 69 of these studies were eliminated after finding duplicates and reviewing the title and abstract. Eleven studies were retrieved, of which six were excluded based on comprehensive full-text review [20-25]. An additional one study was supplemented by searching references [26]. Six studies were ultimately included in the meta-analysis[26-31].

Characteristics of Included Studies The characteristics of the six included studies are shown in Table 1. Two of the trials were performed in South America, two in Asia, and the other were in Africa. Mean ages of patients ranged from 52.70 to 67.08 years and both male and female participants were involved in almost equal proportion. All trials reported balanced baselined characteristics between comparison groups. The outcome measures of Shahin and El-Lakkany[31] were not reported as mean±SD; Marey and Ellakwa[30] did not present VA in logMAR units so that the data could not be pooled in the Meta-analysis. Clinical heterogeneity was seen in several areas such as dosage of drugs or treatment protocols. For example, the intervention of the five studies were a single injection of bevacizumab *vs* one injection of triamcinolone except the study by Lim *et al* [28], whose IVB group was 2 injections of bevacizumab with 6-week intervals.

Table 1 Study characteristics of the included six randomized controlled trials

Study	Country of publication	Major inclusion criteria	Mean age (a)	M/F	No. of eyes	Intervention groups	Duration of follow-up (weeks)	Jadad Score
Paccola 2008	Brazil	Refractory DME and diffuse fluorescein leakage involving the foveal centre and most of the macular area on FFA; BCVA (logMAR) ≥0.3; CMT>300μm	Group 1 65.58±8.44 Group 2 67.08±4.67	Group 1 7/6 Group 2 8/5	Group 1 *n*=13 Group 2 *n*=13	Group 1: IVB (1.5mg) Group 2: IVT (4mg)	1, 4, 8, 12, 24	5
Shimura 2008	Japan	CMT>400μm; VA (logMAR)>0.3	65.70±5.30	8/6	Group 1 *n*=14 Group 2 *n*=14	Group 1: IVT (4mg) Group 2: IVB(1.25mg)	1,24	3
Shahin 2010	Egypt	Diffuse macular edema	52.70	12/20	Group 1 *n*=24 Group 2 *n*=24	Group1: IVT (4mg) Group 2: IVB (1.25mg)	1,4	2
Marey 2011	Egypt	NA	Group 1 57.66±7.19 Group 2 57.66±7.44 Group 3 57.60±7.30	Group 1 18/12 Group 2 19/11 Group 3 16/14	Group 1 *n*=30 Group 2 *n*=30 Group 3 *n*=30	Group1: IVT (4mg) Group 2: IVT/IVB (1.25mg/2mg) Group3: IVB(1.25mg)	1,6,12	1
Lim 2012	Korea	Eyes with clinically significant DME; CMT ≥300μm	Group 1 61.40±6.70 Group 2 58.40±5.90 Group 3 59.80±7.90	Group 1 19/19 Group 2 16/18 Group 3 15/18	Group 1 *n*=38 Group 2 *n*=36 Group 3 *n*=37	Group 1: IVB(2 injections of 1.25mg) Group 2: IVB/IVT (1.25mg/2mg) Group 3: IVT (2mg)	6,12,24,48	5
Isaac 2012	Brazil	CMT>300μm in both eyes, HbA$_{1c}$ of up to 1% above the reference value and BP< 160/90mmHg measured at initial visit	64.60±9.75	6/5	Group1 *n*=11 Group2 *n*=11	Group 1: IVB (1.25mg) Group 2: IVT (4.0mg)	4,12,24	5

DME: Diabetic macular edema; BCVA: Best corrected visual acuity; CMT: Central macular thickness; HbA$_{1c}$: glycosylated haemoglobin; MPC: Macular laser photocoagulation; PDR: Proliferative diabetic retinopathy; PRP: Panretinal photocoagulation; FFA: Fluorescein angiography; DR: Diabetic retinopathy.
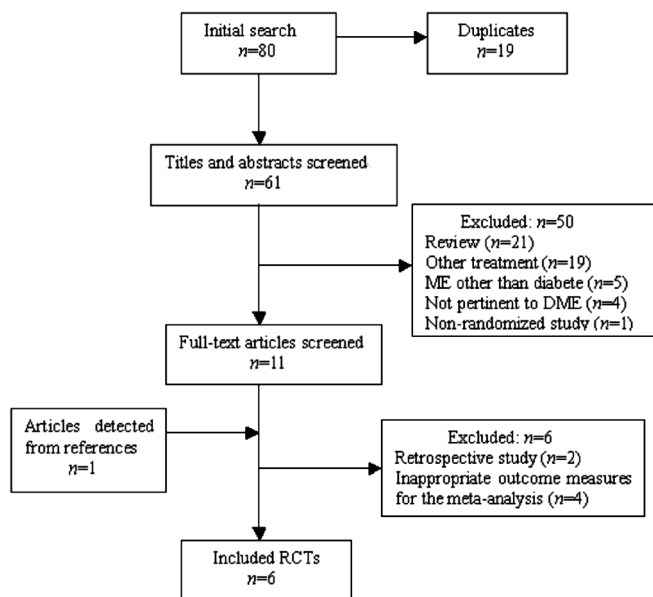
Figure 1 Flow diagram of literatures screening.

Figure 2 Risk of bias summary for each included study (+: low risk of bias; ?: unclear risk of bias; ‑: high risk of bias).

Methodological Quality of Included Studies All the included studies were assessed for methodological quality according to the Jadad score. A risk of bias summary for publication is shown in Figure 2.

Comparing Bevacizumab to Triamcinolone As functional outcome measure, VA was most important for evaluating efficacy. The pooled results revealed that IVT significantly improved VA compared with IVB at 1 month (WMD, -0.10logMAR; 95% CI, -0.14 to -0.06, $P<0.01$) and 3 months (WMD, -0.12 logMAR; 95% CI, -0.16 to -0.08, $P<0.01$). At 6 months, IVT group tended to have more improvement, but the difference was not significant (WMD, -0.08 logMAR; 95% CI, -0.18 to 0.03, $P=0.14$) (Figure 3).

CMT represented the anatomic change after treatment. No significant CMT reduction was detected in the IVT group in comparison with IVB group at 1 month follow-up, although IVT group tended to have greater reduction(WMD, - 47.24μm; CI, -106.79 to 12.31, $P=0.12$). There was significant heterogeneity among trials for this measure of effect ($I^2=88\%$, $P<0.01$). At 3 months follow-up, the reduction in

CMT was still no statistically significant between the two groups and IVT group still tended to have greater reduction (WMD, -36.63μm; CI, -123.28 to 50.02, $P=0.41$). There was substantial heterogeneity among trials for this measure of effect ($I^2=93\%$, $P<0.01$). However, at 6 months follow-up, IVT significantly reduced CMT compared with IVB (WMD, -52.02μm; CI, -70.71 to -33.33, $P<0.01$) (Figure 4).

Intraocular hypertension was reported in IVT group in four studies. The incidence of intraocular hypertension was 13/102 in IVT group during follow-up period while 0/103 in IVB group. The difference was significant (RR, 7.55; CI, 1.78 to 32.06, $P=0.006$) (Figure 5). The intraocular hypertension could be managed with glaucoma medications. No other systematic or intraocular side-effects were noted in either group.

Comparing Bevacizumab+Triamcinolone to Triamcinolone Due to the inadequate data of VA, the meta-analysis could not be assessed. With regards to CMT, no significant difference among groups receiving IVT versus IVB combined with IVT at 1 month (WMD, 3.04μm; CI, -31.29 to 37.36, $P=0.86$) and 3 months (WMD, 76.39μm; CI, -4.09 to 156.88, $P=0.06$) (Figure 6).

Figure 3 Forest plot showing mean difference in VA (logMAR) along with the associated 95% CI in the IVT group versus IVB group A: VA at 1 month; B: VA at 3 months; C: VA at 6 months.

Figure 4 Forest plot showing mean difference in CMT along with the associated 95% CI in the IVT group versus IVB group A: CMT at 1 month; B: CMT at 3 months; C: CMT at 6 months.

The incidence of intraocular hypertension was 6/67 in IVT group during follow-up period while 4/66 in IVB+IVT group. But the difference was not significant (RR, 1.47; CI, 0.44 to 4.95, P=0.53) (Figure 7).

Sensitivity Analysis The study by Lim *et al* [28] compared 2 injections of bevacizumab with 6-week intervals and a single

triamcinolone, which differed from other studies. Removaling of this study has not changed the results.

DISCUSSION
In the studies by Chakrabarti *et al* [25] and Marey and Ellakwa[30], the response to therapy with bevacizumab showed superiority compared with triamcinolone for DME. However, these

| Study or Subgroup | Triamcinolone | | Bevacizumab | | Weight | Risk Ratio | Year | Risk Ratio |
	Events	Total	Events	Total		M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Shahin 2010	4	24	0	24	25.1%	9.00 [0.51, 158.52]	2010	
Marey 2011	2	30	0	30	25.1%	5.00 [0.25, 99.95]	2011	
Isaac 2012	3	11	0	11	25.1%	7.00 [0.40, 121.39]	2012	
Lim 2012	4	37	0	38	24.8%	9.24 [0.51, 165.77]	2012	
Total (95% CI)		102		103	100.0%	7.55 [1.78, 32.06]		
Total events	13		0					

Heterogeneity: Chi² = 0.11, df = 3 (P = 0.99); I² = 0%
Test for overall effect: Z = 2.74 (P = 0.006)

0.005   0.1   1   10   200
Triamcinolone   Bevacizumab

Figure 5 Forest plot showing mean difference in intraocular hypertension along with the associated 95% CI in the IVT group versus IVB group.

A

| Study or Subgroup | Triamcinolone | | | Triamcinolone/Bevacizumab | | | Weight | Mean Difference | Year | Mean Difference |
	Mean	SD	Total	Mean	SD	Total		IV, Fixed, 95% CI		IV, Fixed, 95% CI
Marey 2011	463.2	124.16	30	444.66	131.94	30	28.0%	18.54 [-46.29, 83.37]	2011	
Lim 2012	272	95	37	275	81	36	72.0%	-3.00 [-43.46, 37.46]	2012	
Total (95% CI)			67			66	100.0%	3.04 [-31.29, 37.36]		

Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.17 (P = 0.86)

-200   -100   0   100   200
IVT   IVB/IVT

B

| Study or Subgroup | Triamcinolone | | | Triamcinolone/Bevacizumab | | | Weight | Mean Difference | Year | Mean Difference |
	Mean	SD	Total	Mean	SD	Total		IV, Random, 95% CI		IV, Random, 95% CI
Marey 2011	471.53	148.44	30	348.8	113.25	30	44.0%	122.73 [55.92, 189.54]	2011	
Lim 2012	305	85	37	265	72	36	56.0%	40.00 [3.90, 76.10]	2012	
Total (95% CI)			67			66	100.0%	76.39 [-4.09, 156.88]		

Heterogeneity: Tau² = 2671.49; Chi² = 4.56, df = 1 (P = 0.03); I² = 78%
Test for overall effect: Z = 1.86 (P = 0.06)
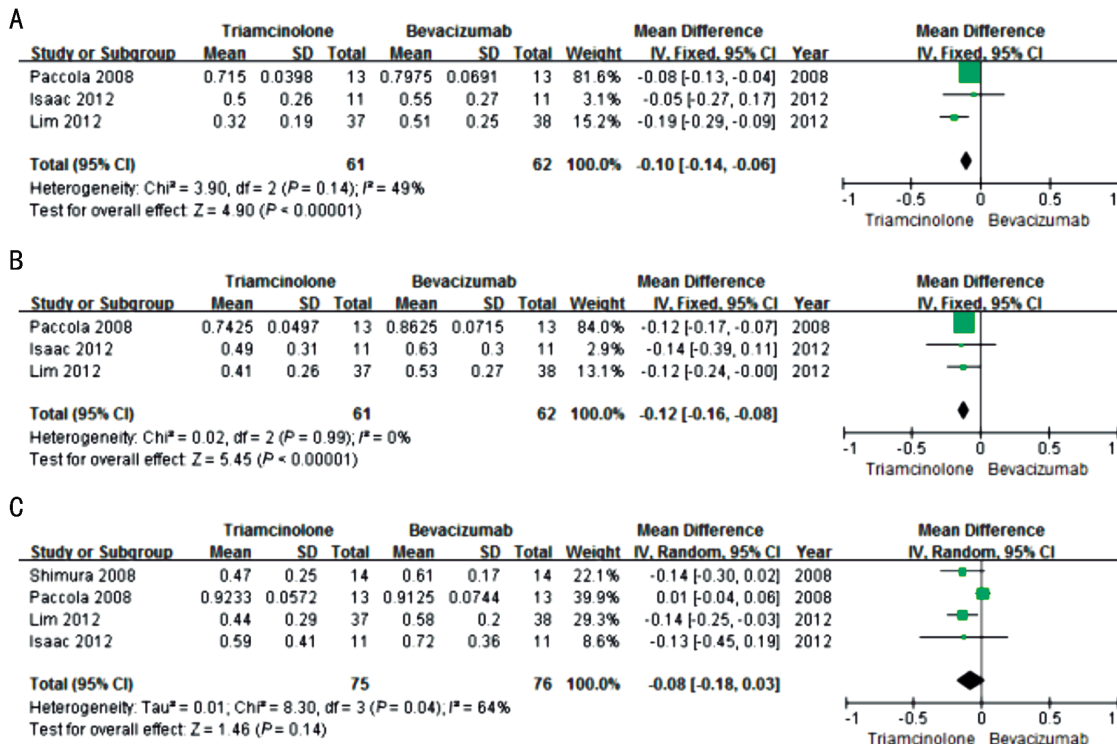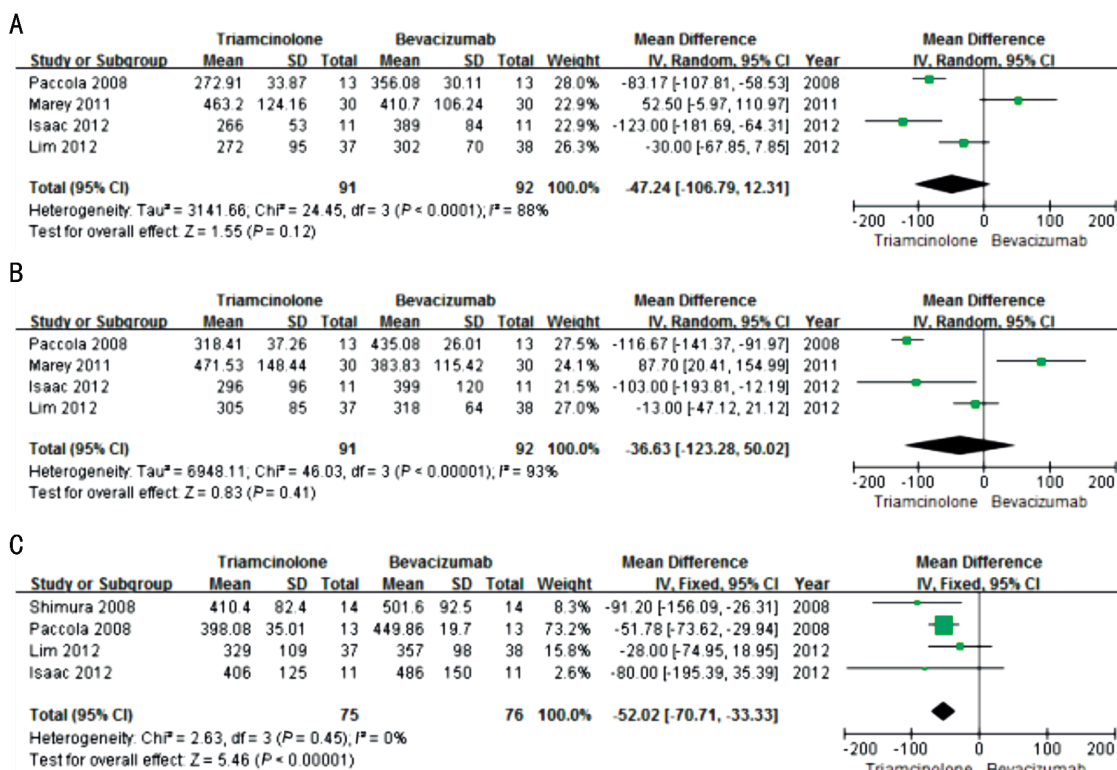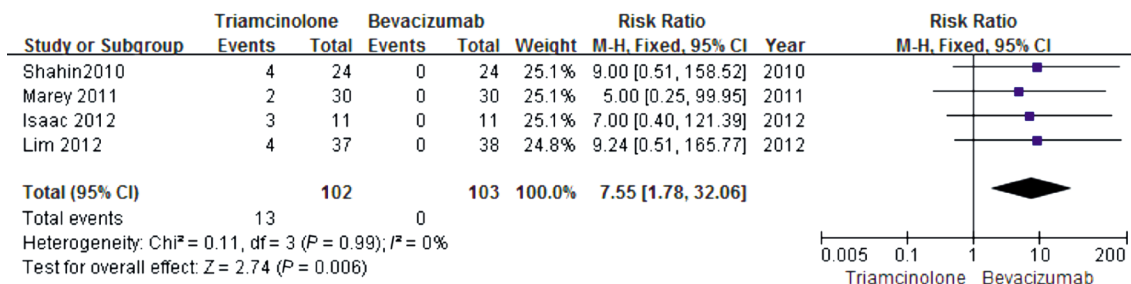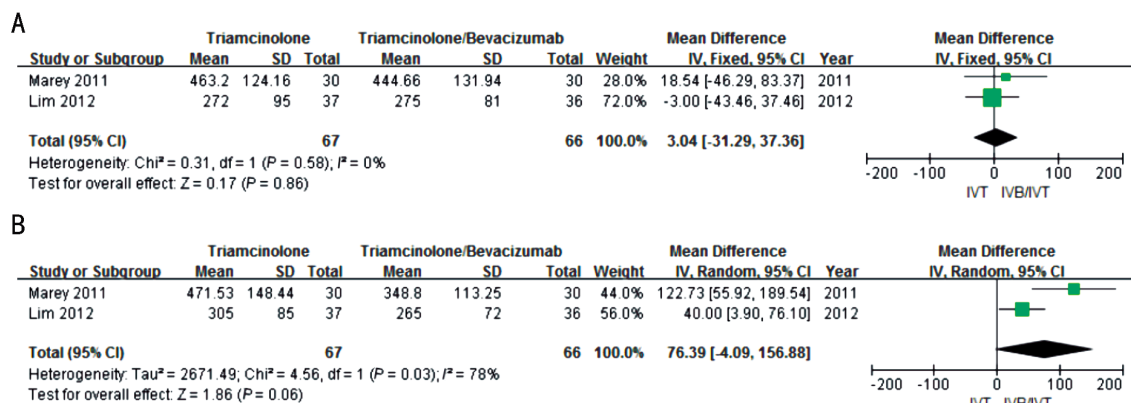
-200   -100   0   100   200
IVT   IVB/IVT

Figure 6 Forest plot showing mean difference in CMT along with the associated 95% CI in the IVT group versus IVB+IVT group A: CMT at 1 month; B: CMT at 3 months.

| Study or Subgroup | Triamcinolone | | Triamcinolone/Bevacizumab | | Weight | Risk Ratio | Year | Risk Ratio |
	Events	Total	Events	Total		M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Marey 2011	2	30	1	30	24.7%	2.00 [0.19, 20.90]	2011	
Lim 2012	4	37	3	36	75.3%	1.30 [0.31, 5.39]	2012	
Total (95% CI)		67		66	100.0%	1.47 [0.44, 4.95]		
Total events	6		4					

Heterogeneity: Chi² = 0.10, df = 1 (P = 0.76); I² = 0%
Test for overall effect: Z = 0.62 (P = 0.53)
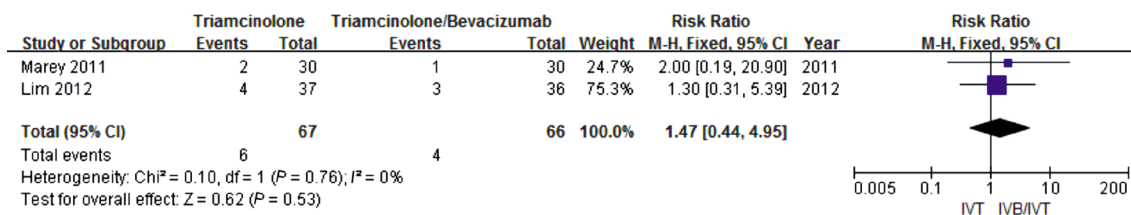
0.005   0.1   1   10   200
IVT   IVB/IVT

Figure 7 Forest plot showing mean difference in intraocular hypertension along with the associated 95% CI in the IVT group versus IVB+IVT group.

studies differed from that of Shimura *et al*[26], Paccola *et al*[29], Isaac *et al* [27] and Lim *et al* [28], who demonstrated that intravitreal triamcinolone was more efficient in reducing DME relative to bevacizumab. And in the other study by Rensch *et al*[32], IVT and IVB did not differ markedly in term of their effects in improving VA and reducing macular thickness. Which treatment is more effective remains controversial. Thus, we conducted this meta-analysis to compare the efficacy of intravitreal triamcinolone and intravitral bevacizumab in DME. As far as we know, this is the first systematic review comparing these two drugs.

In our analysis, we found that the group that received IVT had a statistically significant improvement in vision over the IVB group, and this difference persisted to 3 months. However, the reduction was not significant regarding CMT during the earlier follow-up period (1 month and 3 months). At later visit (6 months), the triamcinolone-treated eyes had a significant decrease in CMT while no significant improvement in VA was observed. These results showed that there was no absolute correlation between anatomic change

(CMT) and functional change (VA). This relation between CMT and VA in DME was discussed by previous studies, which reported a subset of eyes that showed paradoxical increases in CMT with increases in VA or paradoxical decreases in CMT with decreases in VA[33,34]. Browning *et al*[34] pointed out that not only CMT, but age, hemoglobin A1C, and severity of fluorescein leakage in the center and inner subfields were responsible for the change in VA. In another study conducted by Jonas *et al*[35], they concluded the varying degree of macular ischemia may explain why some patients do not show a marked improvement in vision despite a regression of the thickness.

From our results, we showed a favorable response to IVT compared with IVB in improvement of VA at 1 and 3 months. The reason why the difference was not observed in VA at 6 months may be the limited effective time of these two drugs. Many studies have indicated that IVT treatment improved VA at three months but treatment was no longer effective at six months [18,36]. And pharmacokinetic data suggest a single intravitreal injection of 1.25mg bevacizumab

is effective for 6-7 weeks [37]. Thus, a single IVT did not keep its effect to 6 months, so did IVB. There is small number of study comparing the effect of repeating injection of these two drugs and keeping the level of medications in vitreous cavity. Kreutzer *et al* [23] suggested that a single triamcinolone injection may be as effective as a 3 injections of bevacizumab for the treatment of DME. Less number of injections of triamcinolne reduces injection-related complications such as endophthalmitis, decrease burden to the patient and improve the patient compliance. In addition, the cost of treatment with IVT is much lower so IVT seems to be more cost-effective option.

On the other hand, our results demonstrated that the intraocular higher level of VEGF is just one of the pathogenesis of DME. Other mechanisms suppressed by corticosteroid also contribute to it. The conclusion is consistent with previous studies, which indicated various inflammatory mediators that are up-regulated in DME including Tumor Necrosis Fator-α (TNF-α), interleukin-1β (IL-1β) and VEGF play a important role in the pathogenesis of DME [6]. The inflammatory mediators can be modulated with steroids. The angiostatic through inhibition of VEGF and anti-inflammation properties of steroid may make its superiority for DME. Even so, intravitral triamcinolone is gradually losing its leading position as the drug most often used in the treatment of DME since the emerging of anti-VEGF agents. The most important reason is the high rate of complications of IVT including marked elevation of IOP and cataract formation even though no other side-effects were reported in the included studies other than ocular hypertension. To achieve long-lasting concentrations and reduce associated adverse events at high doses of triamcinolone, a novel intravitreal steroid sustained-release device is being introduced into clinic.

We also compared the effect of combination of IVB and IVT versus IVT. The combination of different treatments interest ophthalmologists. The study [38] conducted by the DRCR.net indicated that intravitreal ranibizumab (IVR) or steroid combined with laser photocoagulation produced a rapid and sustained improvement in VA compared with laser alone for DME. It has remained unclear the efficacy of laser photocoagulation combined with anti-VEGF agent versus laser combined with TA. Further clinical trials are needed.

The quality of a systematic review lies on the qualities of included studies. The qualities of the included studies of our analysis are relative high. The results can provide certain reference significance for clinical selection. Even so, there were some limitations of our study. The results in CMT at 1 and 3 months were limited by heterogeneity of the included trials. The differences in the dose of intervention and type of DME may contribute to the clinical heterogeneity. Besides, the included studies all had the characteristics of relative small sample sizes and short duration of follow-up. Several prospective, randomized, blinded and large-sample clinical trials that have been conducted to demonstrate the efficacy and safety of anti-VEGF agents in the management of DME were worth mentioning. The BOLT study [12,39] focused on IVB. The RIDE, RISE[40] and RESTORE studies[41] focused on IVR. The DA VINCI study [42,43] tested the efficacy of VEGF Trap-Eye, which is a VEGF inhibitor whose binding affinity to VEGF is greater than that of bevacizumab and ranibizumab. These studies were well designed.The comparison of repeat injection of IVT and IVB in long duration of follow-up needs multi-center, large sample RCTs.

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