• Meta-Analysis •

Efficiency and safety of laser photocoagulation with or without intravitreal ranibizumab for treatment of diabetic macular edema: a systematic review and Meta-analysis

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Abstract

● AIM: To compare the therapeutic effect and safety of laser photocoagulation along with intravitreal ranibizumab (IVR) versus laser therapy in treatment of diabetic macular edema (DME).

● METHODS: Pertinent publications were identified through comprehensive searches of PubMed, EMBASE, Web of Science, Cochrane Library, and ClinicalTrials.gov to identify randomized clinical trials (RCTs) comparing IVR+laser to laser monotherapy in patients with DME. Therapeutic effect estimates were determined by weighted mean differences (WMD) of change from baseline in best corrected visual acuity (BCVA) and central retinal thickness (CRT) at 6, 12, or 24mo after initial treatment, and the risk ratios (RR) for the proportions of patients with at least 10 letters of improvement or reduction at 12mo. Data regarding major ocular and nonocular adverse events (AEs) were collected and analyzed. The Review Manager 5.3.5 was used.

● RESULTS: Six RCTs involving 2069 patients with DME were selected for this Meta-analysis. The results showed that IVR+laser significantly improved BCVA compared with laser at 6mo (WMD: 6.57; 95% CI: 4.37-8.77; *P*<0.00001), 12mo (WMD: 5.46; 95% CI: 4.35-6.58; *P*<0.00001), and 24mo (WMD: 3.42; 95% CI: 0.84-5.99; *P*=0.009) in patients with DME. IVR+laser was superior to laser in reducing CRT at 12mo from baseline with statistical significance (WMD: -63.46; 95% CI: -101.19 to -25.73; *P*=0.001). The pooled RR results showed that the proportions of patients with at least 10 letters of improvement or reduction were in favor of IVR+laser arms compared with laser (RR: 2.13; 95% CI: 1.77-2.57; *P*<0.00001 and RR: 0.37; 95% CI: 0.22-0.62; *P*=0.0002, respectively). As for AEs, the pooled results showed that a significantly higher proportion of patients suffering from conjunctival hemorrhage (study eye) and diabetic retinal edema (fellow eye) in IVR+laser group compared to laser group (RR: 3.29; 95% CI: 1.53-7.09; *P*=0.002 and RR: 3.02; 95% CI: 1.24-7.32; *P*=0.01, respectively). The incidence of other ocular and nonocular AEs considered in this Meta-analysis had no statistical difference between IVR+laser and laser alone.

● CONCLUSION: The results of our analysis show that IVR+laser has better availability in functional (improving BCVA) and anatomic (reducing CRT) outcomes than laser monotherapy for the treatment of DME. However, the patients who received the treatment of IVR+laser may get a higher risk of suffering from conjunctival hemorrhage (study eye) and diabetic retinal edema (fellow eye).

● KEYWORDS: ranibizumab; diabetic macular edema; laser therapy; anti-vascular endothelial growth factor; Meta-analysis

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INTRODUCTION

Diabetic retinopathy (DR), as a common complication of uncontrolled diabetes, is the leading cause of blindness among working aged individuals in industrialized countries[1]. Vision impairment in patients affected with DR commonly manifests as fluid accumulates beneath the macula which is the central portion of the retina responsible for high visual acuity[2]. Due to microvascular occlusion or microvascular leakage, diabetic macular edema (DME) is the foremost cause of vision impairment in patients with DR[3], which is closely associated to the type and duration of diabetes. According to statistics, the prevalence rate of DME increases from 0 to 3% in individuals with a diagnosis of diabetes to about 30% recently in those with diabetes for over 20y[4]. Other studies propose that because of the patient's age with the type and severity of the diabetes, the 10-year incidence of DME varies from approximately 20% to 40%[5].

In view of the high rise in the number of diabetic patients with DME, effective therapeutic approaches should be widely applied to the treatment of DME indicating to slow the incidence of vision loss and improve the long-term prognosis. For the past several decades, retinal laser photocoagulation has been the mainstay of treatment of DME. Nevertheless, laser therapy has a limited effect in restoring lost vision especially in the severe DME[6]. In recent years, chronically elevated serum glucose has been widely known to damage the retinal-blood barrier (RBB), resulting in upregulation of vascular endothelial growth factor (VEGF)[7], which is the important cause of the development and progression of DME[8]. So an effective therapeutic approach by inhibiting VEGF may be provided for the treatment of DME. Intravitreal anti-VEGF agents, such as ranibizumab, bevacizumab, and aflibercept, have become a useful treatment strategy by acquiring significant improvements in vision and anatomic outcomes in patients with DME. Some randomized clinical trials (RCTs) have elucidated the efficiency of anti-VEGF in the restoration of visual acuity[9].

Ranibizumab (RBZ, Lucentis, Genentech, Inc., San Francisco, CA, USA), the first anti-VEGF agent to be approved by the FDA for treatment, is a humanized monoclonal antibody fragment binding all active forms of VEGF-A[10]. Ranibizumab has been used as an alternative treatment when necessary[11]. Some RCTs have demonstrated that intravitreal ranibizumab (IVR) is importantly more effective than no-control treatment for DME[12]. In view of this, it is necessary to make sure that whether IVR (0.5 mg) together with laser is a more effective and a safer therapeutic approach than laser alone.

A Meta-analysis of RCTs involving IVR for DME has been concentrated on therapeutic effect and safety[13], in which ranibizumab (RBZ) was analyzed together with other anti-VEGF agents. Besides that, there are two studies[14-15] referring to Meta-analysis of RCTs comparing RBZ to laser for DME. But one[14] of the two studies has relatively small sample size because of involving four articles, and the another[15] ignored the adverse reactions of eyes when considering the agent's safety for patient. Thus, this systematic review and Meta-analysis overcome these shortcomings, added the latest RCTs, and then focused on the efficacy and safety of ranibizumab and laser for the patients with visual loss due to DME. The conclusion may provide a useful advice for ophthalmologists to choose appropriate treatment options for the patients with DME in clinical practice.

MATERIALS AND METHODS

Literature Search Five databases (PubMed, EMBASE, Web of Science, Cochrane Library, and ClinicalTrials.gov) were searched for patients from January 2010 to March 2016. Three domains of terms were searched: 1) diabetic macular edema or equivalents (*e.g.* Irvine-Gass syndrome, cystoid macular edema); 2) ranibizumab or equivalents (*e.g.* Lucentis, RhuFab V2); and 3) laser photocoagulation. The keywords from each domain were combined with AND. There was no restriction on language or study design. When titles and/or abstracts fit the index words, the full article was retrieved.

Inclusion and Exclusion Criteria The following criteria were used to include articles for this Meta-analysis: 1) study design: RCTs; 2) intervention: comparing the efficiency and/or safety of IVR+laser treatment to laser photocoagulation alone; 3) population: adult participants (minimum age of 18y) with any type of DME of any sex and race; and 4) reported one or more of the following outcomes: best-corrected visual acuity (BCVA), central retinal thickness (CRT), and adverse events (AEs). The following criteria were used to exclude articles for this Meta-analysis: 1) no full texts, full texts without raw data, review articles, duplicate publications; 2) studies that were not RCTs; and 3) studies of diabetic retinopathy without macular edema. If some articles reported the same trials, only the recent report was included, and data could be obtained from the previous reports.

Data Extraction and Quality Assessment The following data for study characteristics and clinical treatment were extracted from all included studies: 1) basic information: name of first author, the year of publication, location of the study, and design of trials; 2) information of patients: age, gender, duration of follow-up; 3) information of treatment: various intervention groups (including sample number); and 4) outcomes: means and standard deviations (SDs) of value in BCVA and CRT after treatment at a specific follow-up period, the number of major AEs, and so on. Some data not reported in articles could be gotten in ClinicalTrials.gov when necessary. The six studies were analyzed for their bias according to the guidelines described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions*. 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. To be specific, other biases included: an extreme baseline imbalance, risk of bias related to the specific study design used, and trial stopped early due to some data-dependent process. For the above questions of each parameter, a judgment of "yes" 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 5.3.5 software from the Cochrane Collaboration. In this Meta-analysis, continuous data (*e.g.* BCVA) were expressed as means and SDs, and weighted mean differences (WMD) were calculated while dichotomous data

Table 1 Study characteristics of the six trials

Trials (first author, year)	Location	Design	Treatment group (patients, *n*)	Age (mean years)	Gender male, *n* (%)	Follow-up (mo)
Berger A[16], 2015	Canada	RCT	IVR (75)	61.5	42 (56.0)	3, 6, 9, 12
			IVR+laser (73)	60.8	47 (64.4)	
			Laser (72)	62.8	43 (59.7)	
Elman MJ[20], 2015	United States	RCT	IVR+deferred (≥24wk) laser (188)	64	110 (58.5)	12, 24, 36, 60
			IVR+prompt laser (187)	62	102 (54.5)	
			Prompt laser (293)	63	170 (58.0)	
			Triamcinolone+prompt laser (186)	62	100 (53.8)	
Ishibashi T[21], 2015	East Asia	RCT	IVR (133)	60.7	81 (60.9)	12
			IVR+laser (132)	61.2	67 (50.8)	
			Laser (131)	61.5	75 (57.3)	
Mitchell P[23], 2013	Europe, Australia, Canada, Turkey	RCT	IVR (116)	62.9	73 (62.9)	12
			IVR+laser (118)	64.0	70 (59.3)	
			Laser (111)	63.5	58 (52.3)	
Do DV[26], 2013	United States	RCT	IVR (42)	62	13 (31.0)	6, 12, 18, 24, 36
			IVR+laser (42)	62	19 (45.2)	
			Laser (42)	62	20 (47.6)	
Novartis[27], 2012	Germany	RCT	IVR+laser (85)	63.5	53 (62.4)	12
			Laser (43)	63.5	27 (62.8)	

(*e.g.* number of events) were measured as relative risk (RR). Continuous outcomes were reported as mean difference with a 95% confidence interval (CI), and dichotomous outcomes were presented as risk ratio with 95% CI. $P<0.05$ was considered statistically significant. A Chi-square test with P value and the I^2 statistic were used to quantify the statistical heterogeneity between studies. If no heterogeneity between studies was observed ($P>0.1$ or $I^2<50\%$), the fixed effect model was used for the analysis, otherwise the random effect model was used. Forest plots displayed the summary weighted estimates and the funnel plots could be used to assess the publication biases.

RESULTS

Results of Research A total of 366 studies were initially identified according to the index words. Of these, 354 were rejected because of the exclusion criteria. Hence, 12 potential RCTs[16-27] were identified; however, four of them[17-20] reported the same trial called DRCR.net at different time points; the RESTORE study involved two articles[22-23]; and three articles reported the READ-2 study. Therefore, only the recent study of each RCT was chosen for our analysis. In the end, six RCTs were included for the Meta-analysis. Among them, only the one RCT by Novartis[27] has no related articles published, but the outcomes of the RCT could be found at ClinicalTrials.gov. The process of selecting RCTs for the Meta-analysis is shown in Figure 1.

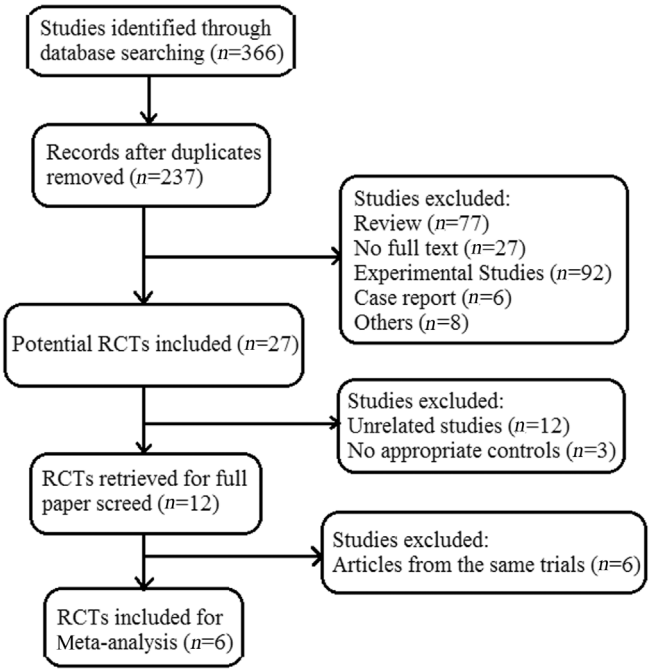

Figure 1 The process of selecting RCTs.

Characteristics of the Eligible Studies Six RCTs with a total of 2069 patients with DME were included in Meta-analysis and the basic characteristics of these studies are shown in Table 1. The sample sizes of different treatment groups varied from 42 to 293 subjects, and durations of follow-up varied from 3 to 60mo. The distribution of age and gender enrolled did not vary significantly between the IVR+laser groups and the laser groups.

Methodological Quality of Included Studies According to the Jadad score, the six included RCTs were assessed for

methodological quality. Assessment of risk of bias summary in included studies about each risk of bias item is shown in Figure 2.

Best Corrected Visual Acuity As essentially functional outcome measure, BCVA was most important for evaluating efficacy. The analysis results of the mean change in BCVA from baseline of each study were presented at 6, 12, 24mo in a forest plot (Figure 3). In the figure, the dots estimate the mean difference; meanwhile, the whiskers extending from the dots show the associated 95% CI. Values to the left of the vertical line at 0 show greater change in BCVA in the subjects of laser group, while values to the right of the vertical line show greater change in IVR+laser group. The subtotal rows show the Meta-analysis summary values for each time point. The pooled results revealed that IVR+laser significantly improved BCVA compared with laser at 6mo (WMD: 6.57; 95% CI: 4.37-8.77; P<0.00001) (Figure 3A), 12mo (WMD: 5.46; 95% CI: 4.35-6.58; P<0.00001) (Figure 3B), and 24mo (WMD: 3.42; 95% CI: 0.84-5.99; P=0.009) (Figure 3C). No heterogeneity was identified at any follow-up point (P=0.57, I^2=0; P=0.64, I^2=0; P=0.45, I^2=0; respectively).

Central Retinal Thickness CRT represented the anatomic change after treatment. The analysis results of CRT of the included studies were presented in a forest plot (Figure 4). Values to the left of the vertical line at 0 show greater change in CRT in the subjects of IVR+laser group, while values to the right of the vertical line show greater change in laser group. The subtotal rows show the Meta-analysis summary values for each time point. The pooled results revealed that IVR+laser significantly reduced CRT compared with laser at 12mo (WMD: -63.46; 95% CI: -101.19 to -25.73; P=0.0010) (Figure 4B) but with substantial heterogeneity (P=0.002, I^2=79%), so a random-effects model was applied to the data. Due to the inadequate data of CRT at 6mo and 12mo, only Berger *et al*[16] reported the results at 6mo and only Elman *et al*[20] reported the results at 24mo, so the Meta-analysis could not be performed. In spite of this, the results at 6mo showed the direction of the effect was favorable for the IVR+laser group with statistical significance (Figure 4A) but the results at 24mo not (Figure 4C).

Secondary Outcomes As for the measured BCVA letters, the analysis results of the pooled RRs comparing the proportion of the patients with at least 10 letters improvement at 12mo were presented in a forest plot (Figure 5). The pooled results showed a significantly higher proportion of patients gaining 10 letters or more in IVR+laser arms compared with laser (RR=2.13; 95% CI: 1.77-2.57; P<0.00001) (Figure 5A) with no heterogeneity identified (P=0.15, I^2=44%). Meanwhile the incidence of loss of at least 10 letters is significantly lower in IVR+laser group than laser group (RR=0.37; 95% CI: 0.22-0.62; P=0.0002) (Figure 5B) with no heterogeneity identified (P=0.15, I^2=48%).

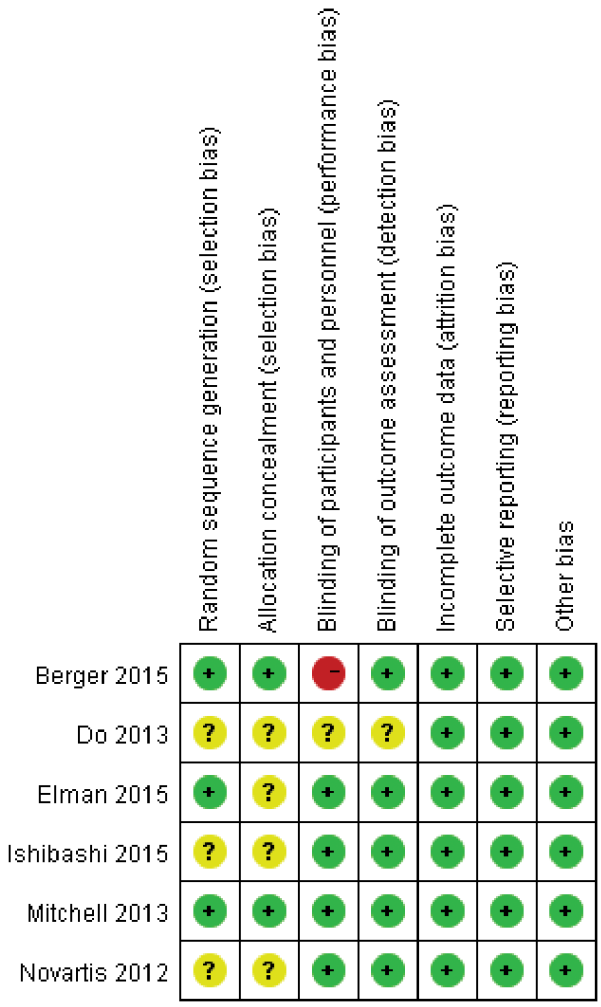

Figure 2 Assessment of risk of bias summary.

Adverse Events Four of six trials included reported the occurrence of AEs in detail. Although DME is a kind of eye disease, the adverse events included ocular AEs (*e.g.* cataract, conjunctival hemorrhage) and nonocular AEs (*e.g.* cardiovascular disorders, infections, and infestations). The incidence of AEs could be one of the most important indices for evaluating the safety comparing IVR+laser to laser. The detailed occurrence of the four trials reporting major ocular and nonocular AEs are described in Table 2.

Figure 6 shows the results of Meta-analysis with statistically significant difference between IVR+laser and laser group in the RR for conjunctival hemorrhage (Figure 6A) and diabetic retinal edema (Figure 6B). Specifically, the RR for conjunctival hemorrhage and diabetic retinal edema were 3.29 (95% CI: 1.53-7.09; P=0.002) and 3.02 (95% CI: 1.24-7.32; P=0.01), respectively, with no heterogeneity identified (P=0.14, I^2=49%; P=0.87, I^2=0; respectively).

As for other five main ocular AEs-cataract, vitreous hemorrhage, eye irritation, eye pain, and dry eye-Figure 7 shows that there was no statistically significant difference in the RR between the two treatment groups. The RR were: 1) 2.35 (95% CI: 0.90-6.15; P=0.08) for cataract (Figure 7A); 2) 0.29 (95% CI: 0.07-1.17; P=0.08) for vitreous hemorrhage (Figure 7B); 3)

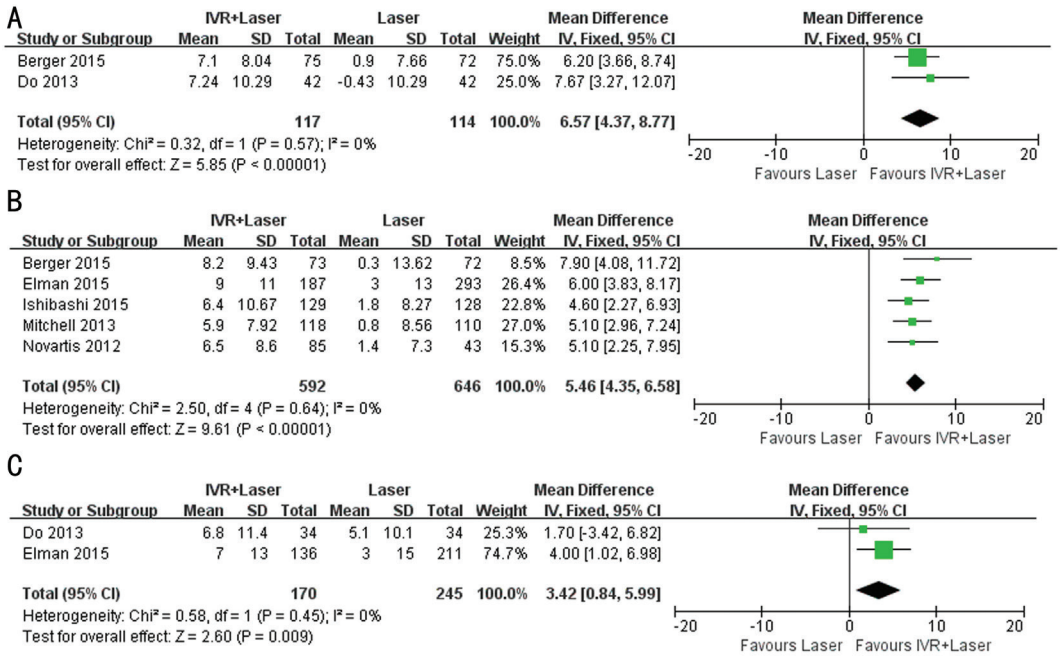

Figure 3 The mean change in BCVA from baseline of each study A: 6mo; B: 12mo; C: 24mo.

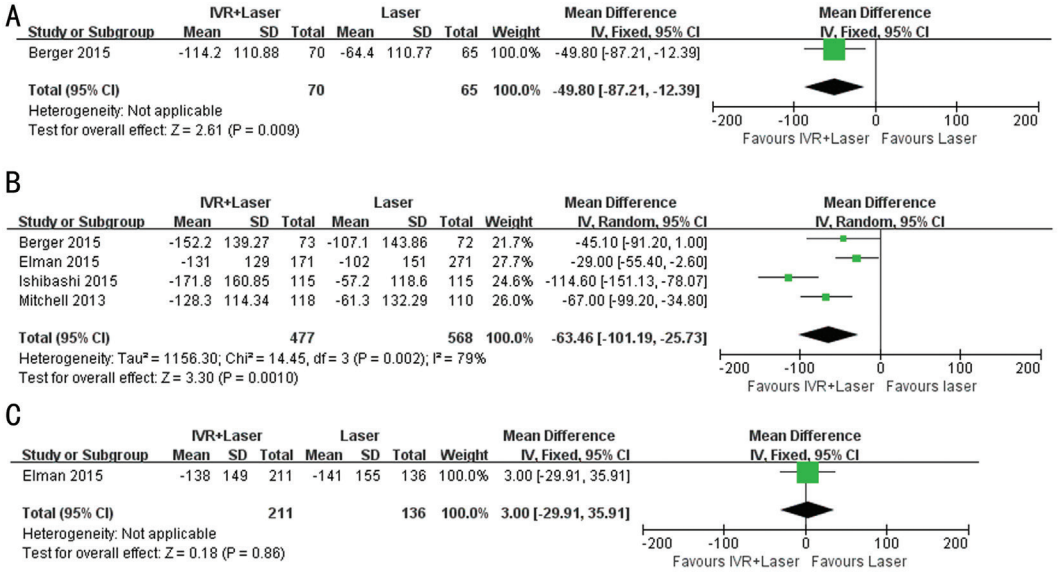

Figure 4 Forest plot of CRT A: 6mo; B: 12mo; C: 24mo.

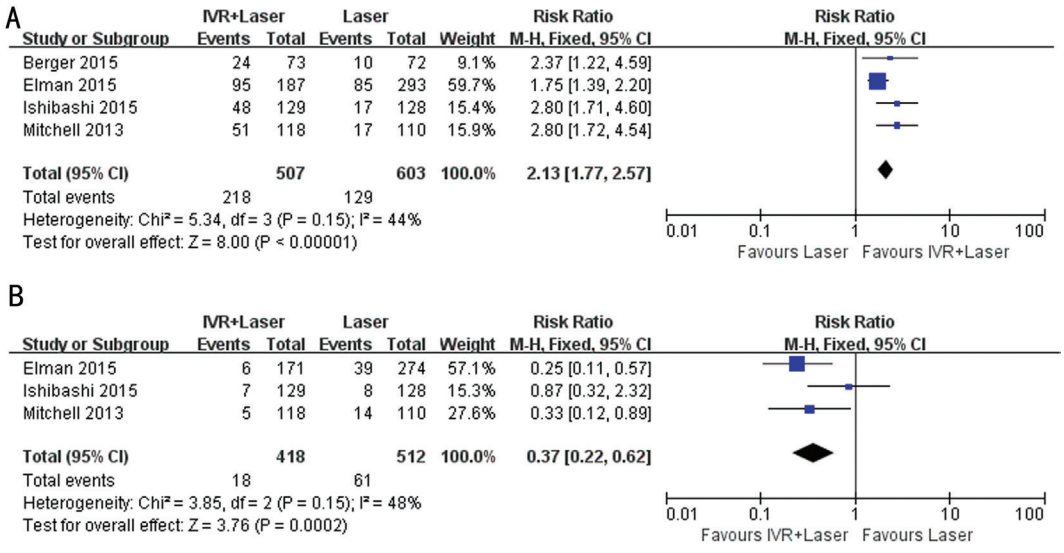

Figure 5 The pooled RRs comparing the proportion of the patients with at least 10 letters improvement at 12mo.

Table 2 Main ocular adverse events and nonocular adverse events

Adverse events	Berger *et al*[16], 2015		Ishibashi *et al*[21], 2015		Mitchell *et al*[23], 2013		Novartis[27], 2012	
	IVR+Laser	Laser	IVR+Laser	Laser	IVR+Laser	Laser	IVR+Laser	Laser
Total	73	74	132	128	120	51	85	43
Serious adverse events	9	5	22	19	43	7	14	5
Ocular adverse events								
Cataract (study eye)			2	0	20	4		
Retinal detachment (study eye)			1	0				
Conjunctival hemorrhage (study eye)	9	1	12	7	13	0		
Vitreous hemorrhage (study eye)	1	6	0	1	1	0		
Eye irritation (study eye)	4	0					5	0
Eye pain (study eye)	3	0			11	2	13	4
Dry eye (study eye)	2	1			4	3		
Diabetic retinal edema (fellow eye)			8	2	20	3	1	0
Nonocular adverse events								
Cardiovascular disorders	1	3	4	1	10	2	1	2
Infections and infestations	7	5	18	12	42	18	15	6
Metabolism and nutrition disorders	2	1	0	4			4	1
Vascular disorders	2	5	8	6	15	6	8	4

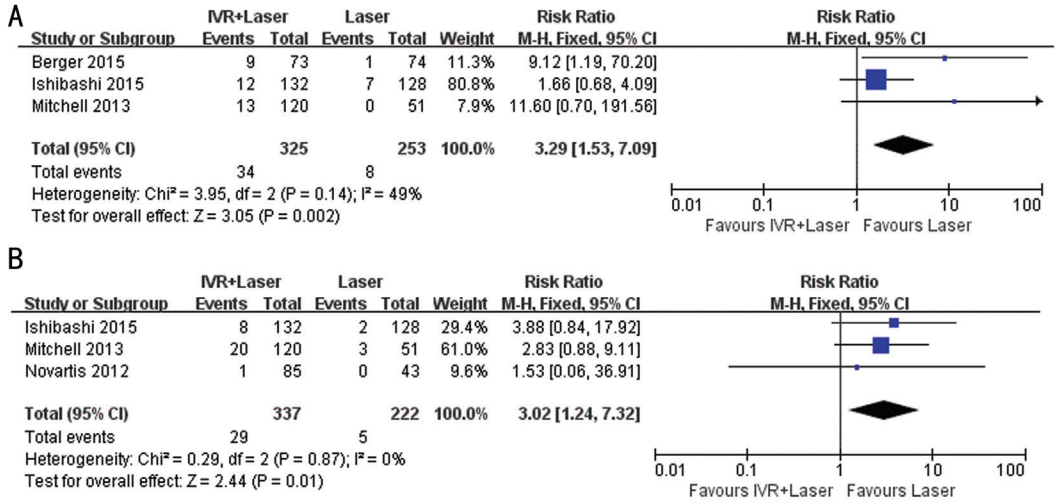

Figure 6 Meta-analysis with statistically significant difference between IVR+laser and laser group in the RR A: Conjunctival hemorrhage; B: Diabetic retinal edema.

7.13 (95% CI: 0.94-54.12; *P*=0.06) for eye irritation (Figure 7C); 4) 2.18 (95% CI: 0.97-4.92; *P*=0.06) for eye pain (Figure 7D); 5) 0.85 (95% CI: 0.26-2.80; *P*=0.78) for dry eye (Figure 7E), all with no heterogeneity identified (*P*=0.61, I^2=0; *P*=0.56, I^2=0; *P*=0.82, I^2=0; *P*=0.64, I^2=0; *P*=0.37, I^2=0; respectively).

Four common nonocular adverse events-cardiovascular disorders, infections and infestations, metabolism and nutrition disorders, and vascular disorders-were also part of the performed Meta-analysis assessment. Figure 8 shows that there was no statistically significant difference in the RR between the two treatment groups. The RR were: 1) 1.22 (95% CI: 0.52-2.89; *P*=0.64) for cardiovascular disorders (Figure 8A); 2) 1.19 (95% CI: 0.85-1.66; *P*=0.31) for infections and infestations (Figure 8B); 3) 0.75 (95% CI: 0.24-2.37; *P*=0.63) for metabolism and nutrition disorders (Figure 8C); 4) 0.98 (95% CI: 0.57-1.67; *P*=0.93) for vascular disorders (Figure 8D), all with no heterogeneity identified (*P*=0.21, I^2=34%; *P*=0.78, I^2=0; *P*=0.20, I^2=37%; *P*=0.69, I^2=0; respectively).

DISCUSSION

Laser photocoagulation, a traditional standard treatment for DME[28], has been widely used for several decades in spite of some limits. Preventing degradation of vision by reducing leaky microaneurysms and inhibiting extravasation of fluid into the macula is the purpose of laser photocoagulation[2]. Until the introduction of anti-VEGF agents, which are known to reduce total retinal thickness, IVR also become an effective

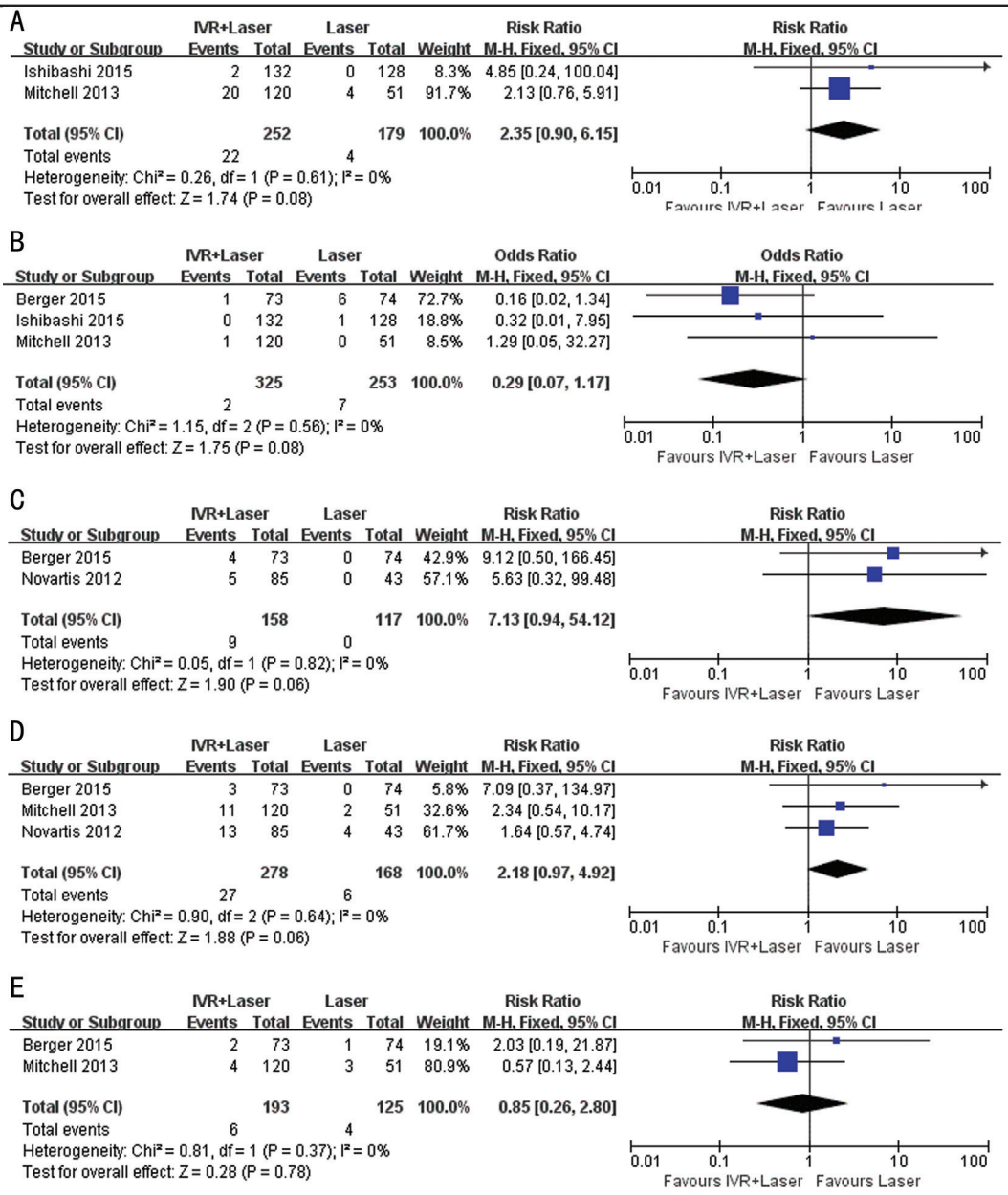

Figure 7 Comparison between IVR+laser versus laser for the incidence of five ocular adverse events in patients with DME A: Cataract; B: Vitreous hemorrhage; C: Eye irritation; D: Eye pain; E: Dry eye.

therapeutic strategy for DME. It has been reported that the significant reduction of the plasma levels of VEGF in patients with DME were found after the intravitreal injection of ranibizumab[29]. Hence, the treatment of laser with ranibizumab is theoretically more advantageous in restoring visual function than laser alone.

Based on six RCTs enrolled in this Meta-analysis, the results demonstrated that IVR+laser could acquire significant improvement in BCVA at 6, 12, and 24mo, as well as reduction in CRT at 12mo compared with the treatment of laser monotherapy. According to secondary outcomes, the treatment of IVR+laser also manifested the superiority for DME because of the higher proportion of patients gaining at least 10 letters and the lower proportion losing at least 10 letters. These results assessing functional and anatomic index had statistical differences between the two treatment groups, which showed that IVR+laser therapy had a significantly better effect for patients with visual impairment due to DME than laser monotherapy.

Although IVR therapy is a general effective treatment stagey, it is an invasive intervention of the eye, which may lead to a relatively higher risk of ocular AEs. Due to any ocular AE in the previous Meta-analysis[14-15], especially conjunctival hemorrhage, the statistical differences were denied or not mentioned between two treatment groups because of limitations of statistical data at that time. Now the major ocular AEs showed in the Meta-analysis were conjunctival hemorrhage, vitreous hemorrhage, cataract, eye irritation, eye pain, dry eye, and diabetic retinal edema (fellow eye). As Meta-analysis for these ocular AEs clarified, it is statistically significant compared to the laser monotherapy that conjunctival hemorrhage (study eye) and diabetic retinal edema (fellow eye)

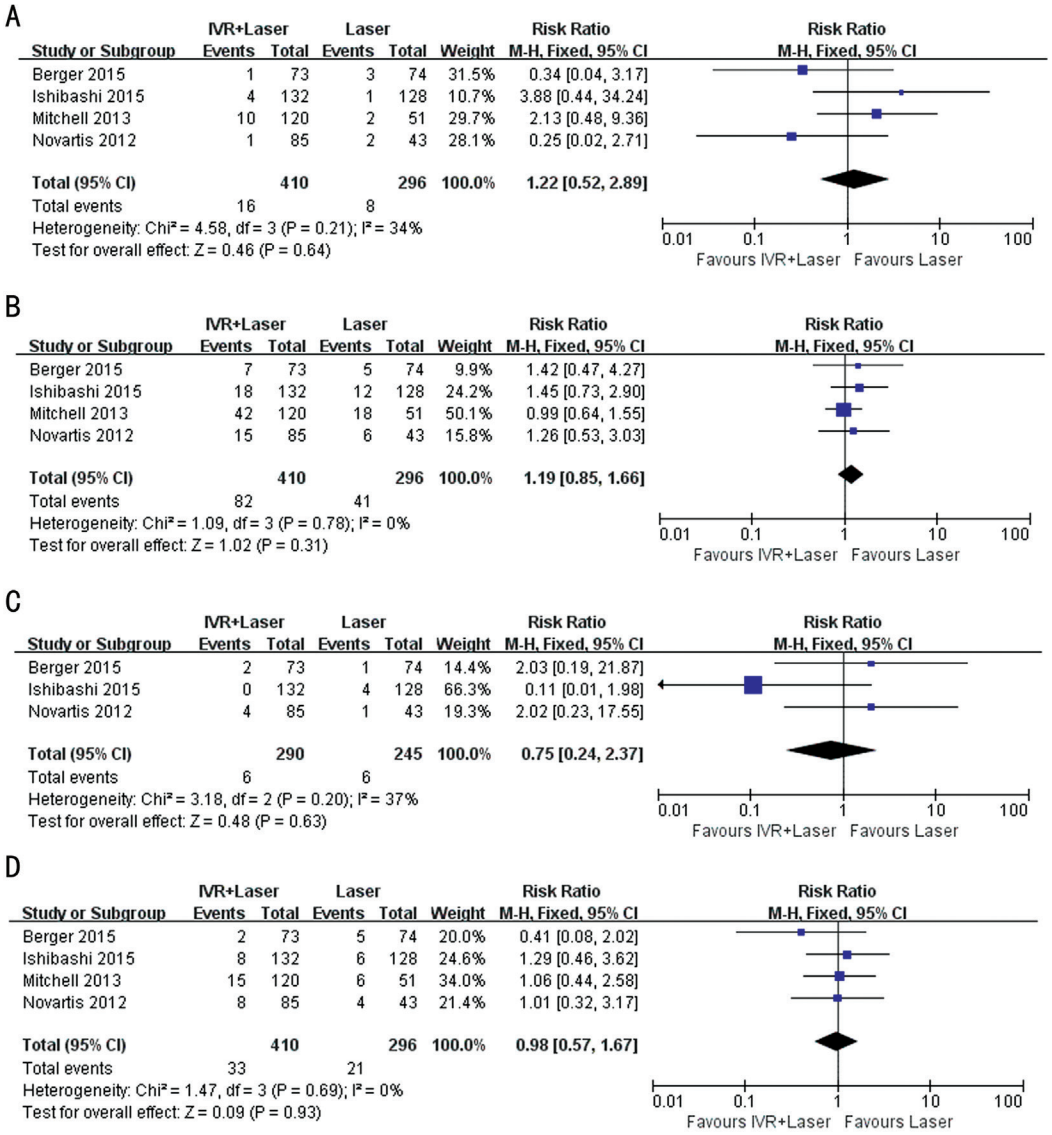

Figure 8 Comparison between IVR+laser versus laser for the incidence of four non-ocular adverse events in patients with DME A: Cardiovascular disorders; B: Infections and infestations; C: Metabolism and nutrition disorders; D: Vascular disorders.

occurred at a higher proportion of patients in IVR+laser group. Contraposing other five ocular AEs as mentioned above, there were no statistical difference between the two groups.

Moreover, ranibizumab, including other anti-VEGF drugs, when delivered into the vitreous and passed into the systemic circulation, had a possibility of resulting cardiovascular events, infections and infestations, vascular disorders, and so on[30]. Especially for cardiovascular events and vascular disorders, the two AEs were also a little more common in patients with DME treated with ranibizumab in RISE and RIDE studies[31]. Nevertheless, there were no significant differences observed with respect to the proportion of the nonocular AEs as mentioned above due to the present data. The normal range of VEGF in the systemic circulation is necessary for normal physiological function. Considering that ranibizumab could bind to all the isoforms of human VEGF-A[32], so may ranibizumab bring negative impact normal physiological functions. However, Gaudreault *et al*[33] found that the agent failed to be detected in the contralateral eye and its content was particularly low in the serum. Also when ranibizumab was used for other age-related macular degeneration, the agent has been proven safe without statistical data about nonocular AEs[34-36]. From what has been discussed above, IVR+laser therapy could be safe in the treatment of DME compared to the laser alone treatment when considering nonocular AEs.

In summary, the results of this Meta-analysis have given statistically significant conclusions that IVR+laser is relatively superior to laser according to the functional (improving BCVA) and anatomic (reducing CRT) outcomes at the follow-up time points. In spite of some ocular AEs happening, IVR+laser was still considered as the effective treatment approach for DME weighing the advantages and disadvantages. Besides that, as compared with laser alone, laser photocoagulation combined with intravitreal steroid agents also could be a better therapeutic strategy in terms of CRT reduction and 1-month earlier visual improvement for patients with DME[37].

In this Meta-analysis, the data from enrolled trails were not reported in all follow-up points, and most trials offered the outcomes at 12mo. Hence, more data in all follow-up phases and more RCTs should be required to improve the accuracy and robust of the Meta-analysis which can provide some guidance suggestions in the clinical.

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