• Meta-Analysis •

Bevacizumab as adjuvant therapy in the management of pterygium: a systematic review and Meta-analysis

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Abstract

• AIM: To evaluate the clinical effect of bevacizumab in pterygium treatment.

• METHODS: A systematic review and quantitative Meta-analysis was performed. PubMed, EMBASE, Web of Science and Cochrane database were searched for eligible literatures published in English until June 2016. The endpoint was recurrence rate and pooled risk ratio (RR) was calculated.

• RESULTS: Nine eligible studies were included and Meta-analysis results showed no significantly difference in patients treated with bevacizumab in short term follow-up [3mo: RR=0.70 (0.34, 1.45); 6mo: RR=0.55 (0.23, 1.32)] compared with control groups. No significant effects were observed in favor of bevacizumab in subgroup analyses: patients with subconjunctival injection of bevacizumab [3mo: RR=0.95 (0.70, 1.29); 6mo: RR=0.83 (0.55, 1.28)], primary pterygium [3mo: RR=0.59 (0.23, 1.54; 6mo: RR=0.59 (0.23, 1.53)], simple pterygium excision [3mo: 0.32 (0.05, 2.04), *P*=0.23; 6mo: 0.27 (0.05, 1.53)] and excision with conjunctival autograft [3mo: 1.51 (0.25, 9.15); 6mo: 1.11 (0.06, 21.69)].

• CONCLUSION: In this Meta-analysis, we did not found the significant effect of bevacizumab in pterygium treatment, at least in short term follow-up (3mo and 6mo).

• KEYWORDS: pterygium; bevacizumab therapy; recurrence; Meta-analysis

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INTRODUCTION

Pterygium is a chronic disease of the ocular surface, which is associated with inflammation and neovascularization. It features the invasive centripetal proliferation of fibrovascular tissue mostly on the nasal aspect of bulbar conjunctiva. Although a number of surgical techniques have been described as methods for pteryigium treatment, including bare sclera resection, excision plus rotational conjunctival flap, and excision with conjunctival autograft placement, the recurrence rate remains high after surgery. In following discussion, the definition of pterygium recurrence referred to Tseng's criteria, which with fibrovascular tissue invading the cornea[1].

Several studies suggested vascular endothelial growth factor (VEGF) is over expressing and plays an important role in development of pterygium[2-4]. This led to the hypothesis that the application of anti-VEGF agent could be beneficial for patients with pterigium. Bevacizumab, a recombinant human monoclonal antibody against VEGF which is approved by FDA in several neoplasms therapy, showed a promising role in both retinal disease and eye surface disease by off-label use. Several clinical trials were conducted to evaluate the effect of bevacizumab in pterygium treatment. However, the outcomes were still limited and controversial. In this review, we sought to investigate whether bevacizumab could decrease the reccurence rate in pterygium patients.

MATERIALS AND METHODS

Search Strategy Articles about "pterygium OR pterygia therapy AND bevacizumab" were searched in PubMed, EMBASE, Web of Science and Cochrane Controlled Trials Register before June 2016 by two reviewers (Liu J and Liang GL) independently. Only English language articles were included. We also searched the bibliographies of retrieved articles for potentially relevant articles.

Including and Excluding Criteria We included randomized controlled trials (RCTs) that met the following inclusion criteria: 1) evaluated the efficacy of bevacizumab in patients with pterygium; 2) compared with control group either negative or blank; 3) defined pterygium recurrence as fibrovascular tissue invading the cornea; 4) assessed the recurrence in the outcomes; 5) provided enough data for calculating the risk ratio (RR) and 95% confidence interval (CI); 6) the one with complete data if studies were duplicates. Exclusion criteria were: 1) duplicate research; 2) reviews, letters and comments; 3) follow-up was shorter than 3mo; 4) low quality clinical trials.

Data Abstraction and Quality Assessment Two reviewers independently retrieved the eligible studies according to the search strategy and selection criteria. The manual search was performed to retrieve some more eligible studies in the reviews and references of included studies. After article identification, characteristics of studies and patients such as first author, publication year, age and gender of patients, type of pterygium, sample size, pterygium length, intervention method, follow-up period, outcome assessment and study location were extracted independently. Discrepancies in data abstraction were resolved by referring to the original article.

Study quality was assessed by Jadad scale, which contains evaluation of randomization, blinding, participant withdrawals/dropouts. If randomization and blinding were appropriate, additional point was added for each. The quality score ranges from 0 to 5 points. When the score of article <3, it was considered to be low quality. The risk of bias in RCTs was assessed following cochranere commendations and publication bias was evaluated by Egger test (Stata version 10.0). Publication bias was indicated when *P* value was less than 0.1.

Statistical Analysis The result was reported as a pooled RR with 95% CI. Statistical heterogeneity was tested using the χ^2 and I^2 statistic. Fixed-effects model was used by Mantel-Haenszel method unless significant evidence of statistical heterogeneity or clinical diversity was found. However, for result showing significant heterogeneity (I^2>50%), a random-effects Meta-analysis was performed by DerSimonian-Laird method[5]. *P* value<0.05 was considered statistically significant difference. The Meta-analysis was done consists with recommendations from the Cochrane Collaboration and the PRISMA Statement with standard software (Revman 5.0 and Stata version 10.0)[6]. The PRISMA checklist was guided the overall conduct of this study.

RESULTS

Characteristics and Quality Assessment of Eligible Studies Up to June 2016, 54 records were finally retrieved using the search strategy and after removing duplication. Reviewing the titles and abstracts, there were 23 studies left for full text reviewed and quality assessment. With careful evaluation according to our eligibility criteria, 5 studies were excluded for without negative control[7-11], 5 studies for without exact information about recurrence[12-16], 2 articles for different definitions of recurrence[17-18] and 2 articles for low quality[19-20]. Finally, 9 controlled clinical trials with 496 participants were included in this Meta-analysis (Figure 1). The main characteristics of RCTs were listed in Table 1.

The included articles were published from 2011 to 2016, originated from Thailand, Iran, Egypt, Turkey, Mexico and India. Quality assessment was conducted according to Jadad scale and Cochrane Collaboration's tool. The biases in these studies were showed in Figure 2.

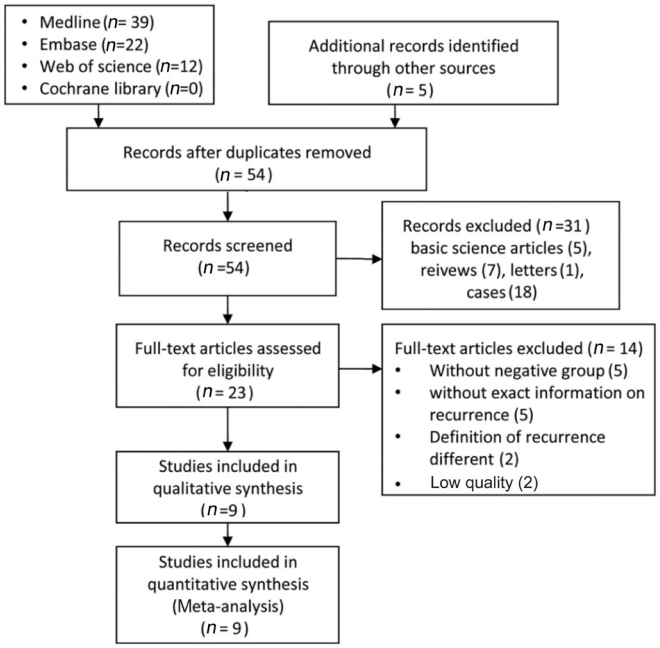

Figure 1 The flowchart for systematic literature search.

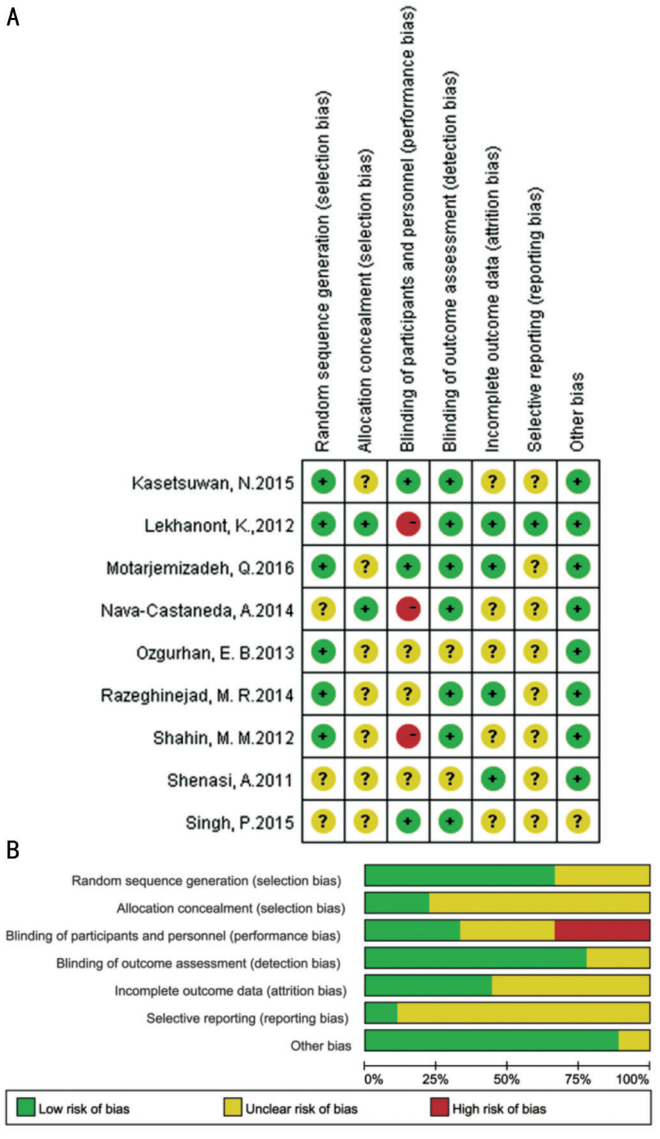

Figure 2 Assessment of risk of bias A: Risk of bias summary: each randomized trial assessed by Cochrane Collaboration's tool; B: Risk of bias graph: each risk of bias item presented as percentage across all included randomized trials.

Table 1 The main characteristics of randomized clinical trials

First author and publication year	Patients No.	Age	Genders (M/F)	Type of pterygium	Arms	Surgery
Motarjemizadeh Q[21], 2016	30	40.97±7.34	17/13	Primary	Placebo group, 4 times daily for 1wk postoperatively	BS
	30	39.90±7.07	16/14	Primary	Bevacizumab 5 mg/mL topical, 4 times daily for 1wk postoperatively	BS
	30	39.03±6.79	11/19	Primary	Bevacizumab 10 mg/mL topical, 4 times daily for 1wk postoperatively	BS
Singh P[22], 2015	30	NR	NR	Primary	Subconjunctival normal saline 1.25 mg/0.05 mL	ECA
	30	NR	NR	Primary	Subconjunctival bevacizumab 1wk before surgery 1.25 mg/0.05 mL	ECA
Kasetsuwan N[23], 2015	10	59.30±11.3	5/5	Primary	Placebo group, 4 times daily for 3mo postoperatively	BS
	12	50.70±10.4	5/7	Primary	Bevacizumab 0.05% topical, 4 times daily for 3mo postoperatively	BS
Razeghinejad MR[24], 2014	22	44.13±12.27	11/11	Primary	Subconjunctival BSS 0.2 mL at the end of surgery	ERC
	22	41.95±12.01	12/10	Primary	Subconjunctival bevacizumab 5 mg/0.2 mL on the day of surgery and 2.5 mg/0.1 mL on the fourth day after surgery	ERC
Nava-Castaneda A[25], 2014	16	47.80±15.6	3/13	Primary	Blank control group	ECA
	17	45.70±16.3	4/13	Primary	Subconjunctival bevacizumab 2.5 mg/0.1 mL applied after surgery, with another same dose 15d after surgery	ECA
	16	51.80±14.5	4/12	Primary	Subconjunctival bevacizumab 2.5 mg/0.1 mL at the end of surgery	ECA
Ozgurhan EB[26], 2013	22	50.50±17.8	6/16	Recurrent	1mo after surgery, artificial tear 4 times daily for 2mo	ECA
	22	48.40±11.3	4/18	Recurrent	1mo after surgery, 5 mg/mL topical bevacizumab 4 times daily for 2mo	ECA
Shahin MM[27], 2012	21	57.58±4.89	11/10	Primary	Blank control group	ECA
	20	58.40±5.04	13/7	Primary	Subconjunctival bevacizumab 1.25 mg/0.05 mL at the end of surgery	ECA
Shenasi A[28], 2011	33	55.94±12.68	25/8	Primary	Subconjunctival distilled water at the end of surgery	BS
	33	58.67±14.60	27/6	Primary	Subconjunctival bevacizumab 1.25 mg/0.05 mL at the end of surgery	BS
Lekhanont K[29], 2012	20	48.27±11.21	11/9	Impending recurrent	Blank control group	BS or ECA
	20	49.80±11.55	10/10	Impending recurrent	Intralesional injection bevacizumab 1.25 mg/0.05 mL	BS or ECA
	20	47.55±10.84	11/9	Impending recurrent	Intralesional injection bevacizumab 2.5 mg/0.05 mL	BS or ECA
	20	49.60±10.92	9/11	Impending recurrent	Intralesional injection bevacizumab 3.75 mg/0.05 mL	BS or ECA

NR: Not reported; BS: Bare sclera; ECA: Excision with conjunctival autograft; ERC: Excision with rotational conjunctival flap. Blank control means same treatment except bevacizumab.

Analysis of Recurrence We analyzed the recurrence in patients with bevacizumab intervention versus placebo/no intervention according to different follow-up periods. Pooled results of 3mo and 6mo were comparable between bevacizumab intervention versus placebo/no intervention [3mo: RR=0.70 (0.34, 1.45); 6mo: RR=0.55 (0.23, 1.32)]. However, decreased recurrence rate was observed at 1y follow-up [RR=0.14 (0.05, 0.36)]. Because of the significant homogeneity for 6mo follow-up and total data (6mo: P=0.18, I^2=61%; Total data: P=0.02, I^2=69%), the analysis was performed by a random-effects model. The totally pooled RR was 0.51 (0.29, 0.88). Egger test did not indicate obvious publication bias. The pooled analysis indicated that bevacizumab did not significantly decrease the recurrence rate of pterygium (Figure 3).

Analysis of Recurrence in Patients with Subconjunctival Injection Among included trails, 6 studies were performed

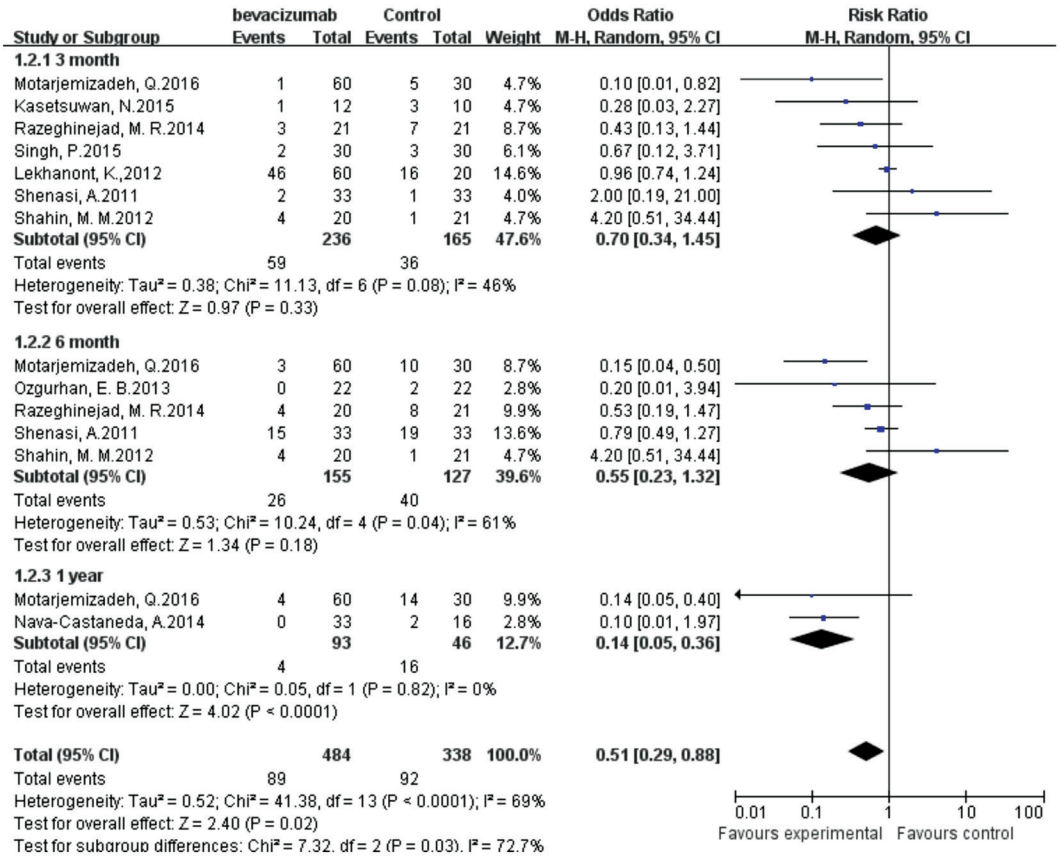

Figure 3 Forest plot for recurrence in patients with bevacizumab intervention versus placebo/no intervention based on a random-effects model.

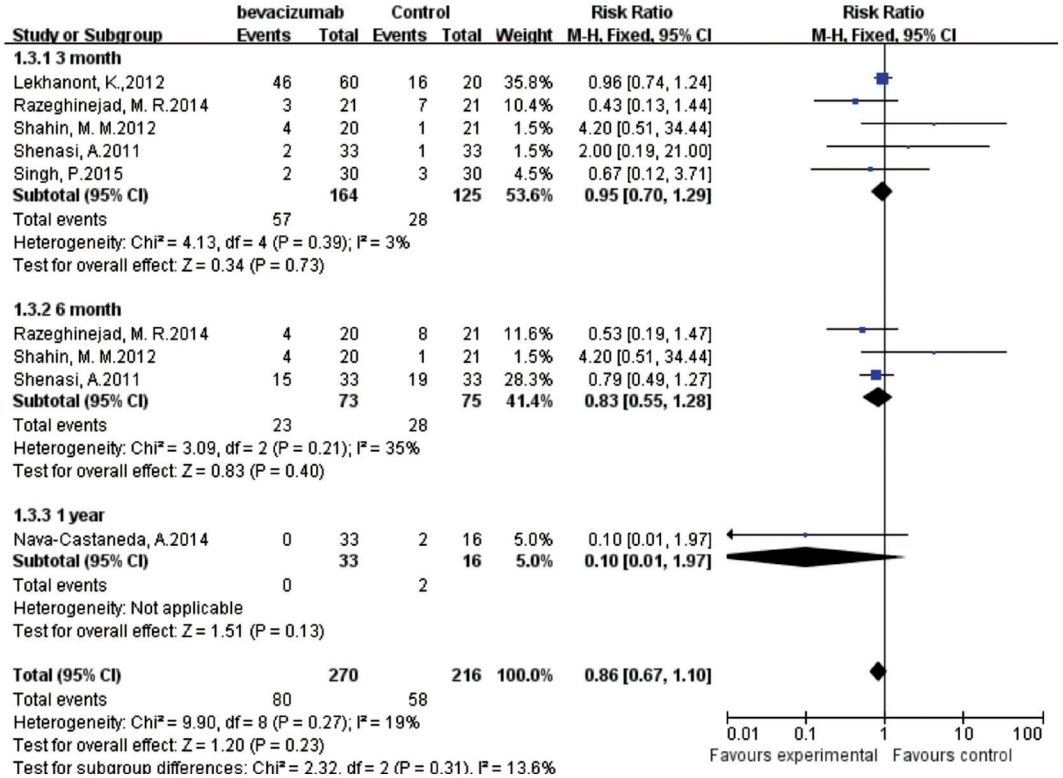

Figure 4 Forest plot for pteygium recurrence in subconjunctival bevacizumab injection group and control group.

with subconjunctival injection. The pooled results revealed similar recurrence between bevacizumab versus control group [3mo: RR=0.95 (0.70, 1.29); 6mo: RR=0.83 (0.55, 1.28)]. No significant heterogeneity was observed among all studies (3mo: P=0.39, I^2=3%; 6mo: P=0.21, I^2=35%) and fixed-effects model was used (Figure 4).

Furthermore, we compared patients who accepted 1.25 mg/0.05 mL bevacizumab subconjunctival injection with those

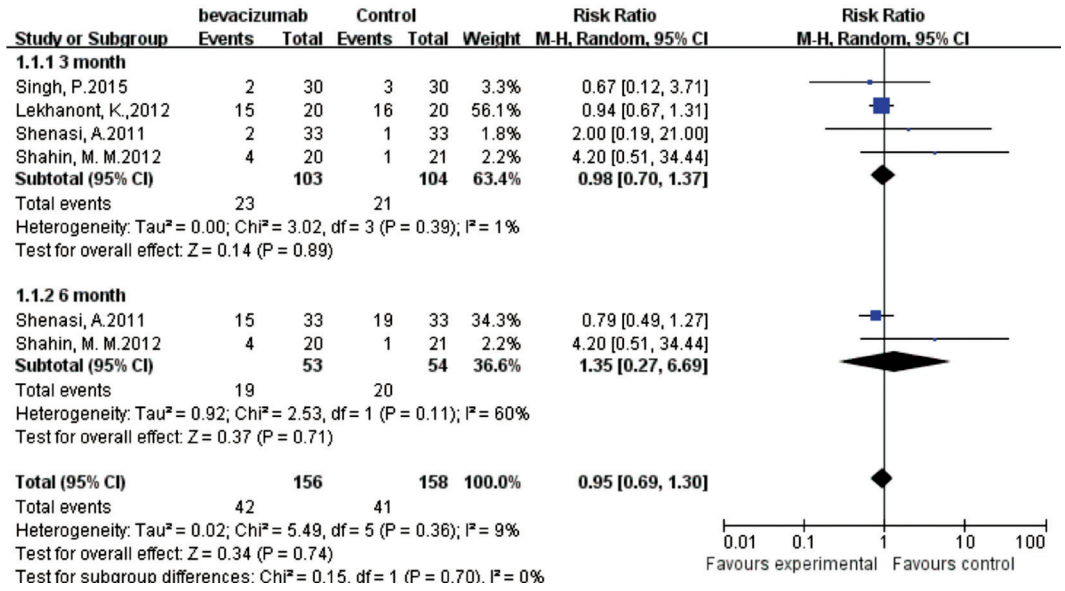

Figure 5 Forest plot for pteygium recurrence in 1.25 mg/0.05 mL subconjunctival bevacizumab injection group and control group.

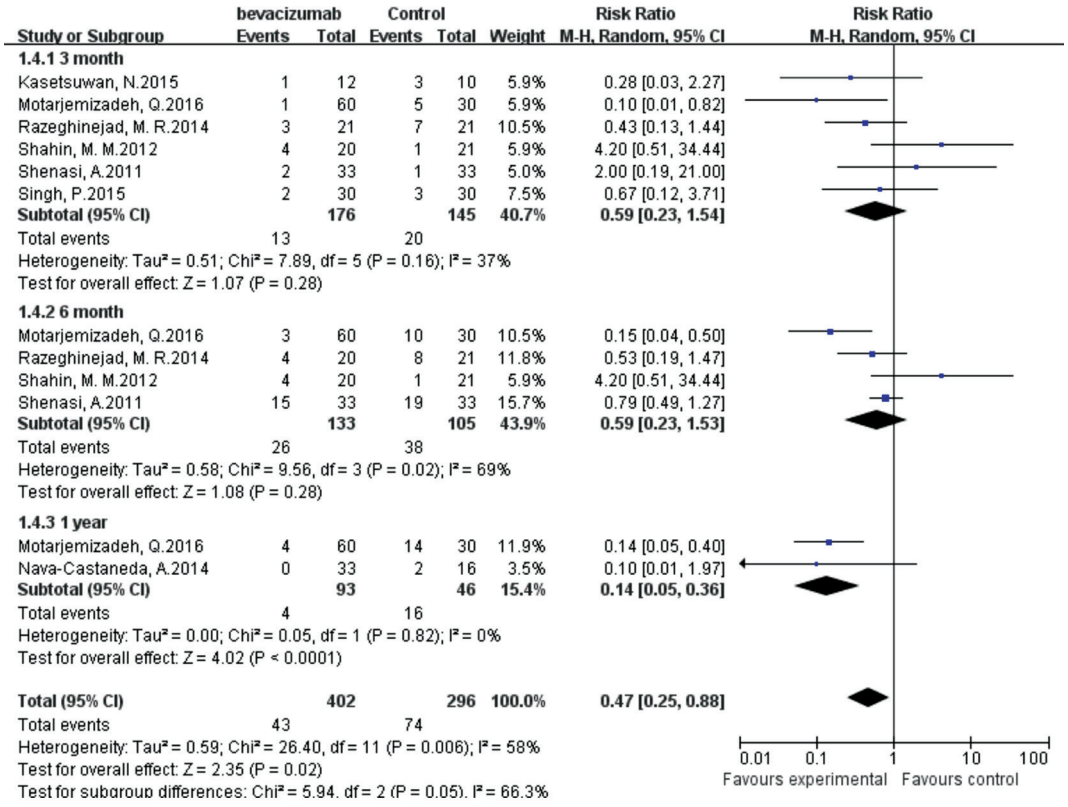

Figure 6 Forest plot for recurrence of patients with primary pterygiumin bevacizumab group versus control group.

without anti-VEGF therapy. No significant difference in recurrence rate was observed either [3mo: RR=0.98 (0.70, 1.37); 6mo: RR=1.35 (0.27, 6.69)]. Moderate heterogeneity was observed in 6mo follow-up (P=0.11, I^2=60%) and random-effects model was used (Figure 5).

Analysis of Recurrence of Patients with Primary Pterygium In analysis for primary pterygium, 6 studies (321 participants), 4 studies (238 participants) and 2 studies (139 participants) were assessed at 3mo, 6mo and 1y respectively. Compared with control group, pooled RR was 0.59 (0.23, 1.54) for 3mo, 0.59 (0.23, 1.53) for 6mo and 0.14 (0.05, 0.36) for 1y. The test of homogeneity showed moderate heterogeneity for total data (3mo: P=0.16, I^2=37%; 6mo: P=0.02, I^2=69%; 1y: P=0.82, I^2=0; total: P=0.006, I^2=58%) and outcomes were analyzed by random-effects model (Figure 6).

Analysis of Recurrence of Patients with Simple Pterygium Excision and Excision with Conjunctival Autograft In all of included studies, bevacizumab was performed as adjuvant therapy with surgery such as excision with conjunctival autograft, excision with rotational conjunctival flap or excision by bare sclera technique. To avoid the influence of surgery routine, we made analysis of simple excision and excision with conjunctival autograft surgery. Pooled results showed no difference between bevacizumab intervention versus placebo/

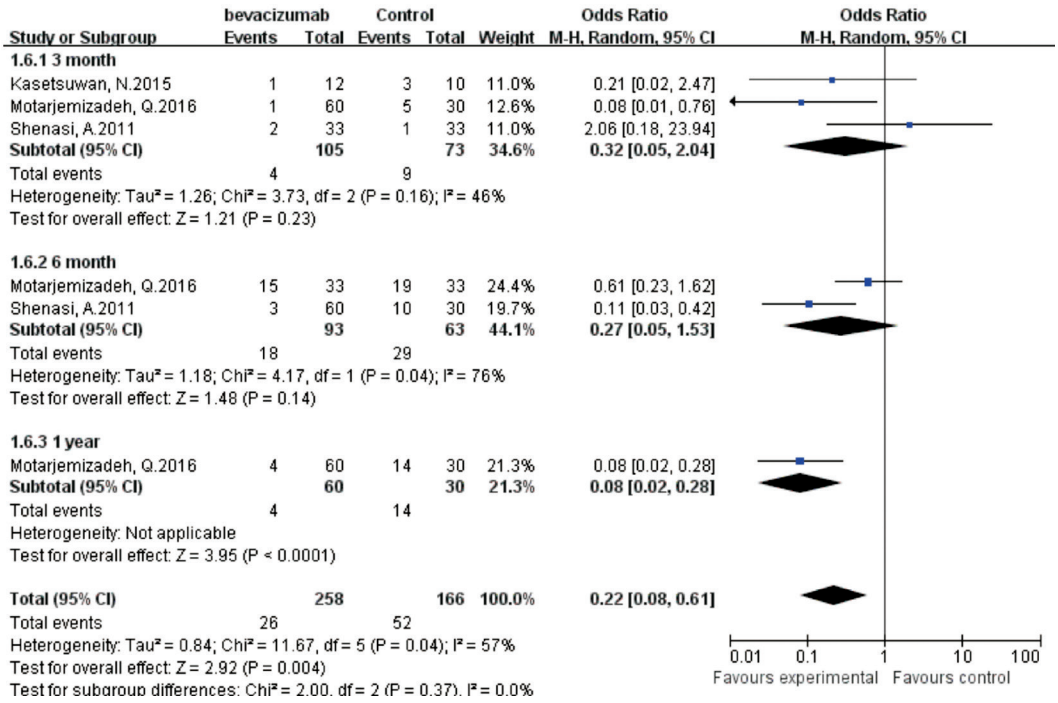

Figure 7 Forest plot for recurrence of patients with simple excision in bevacizumab group versus control group.

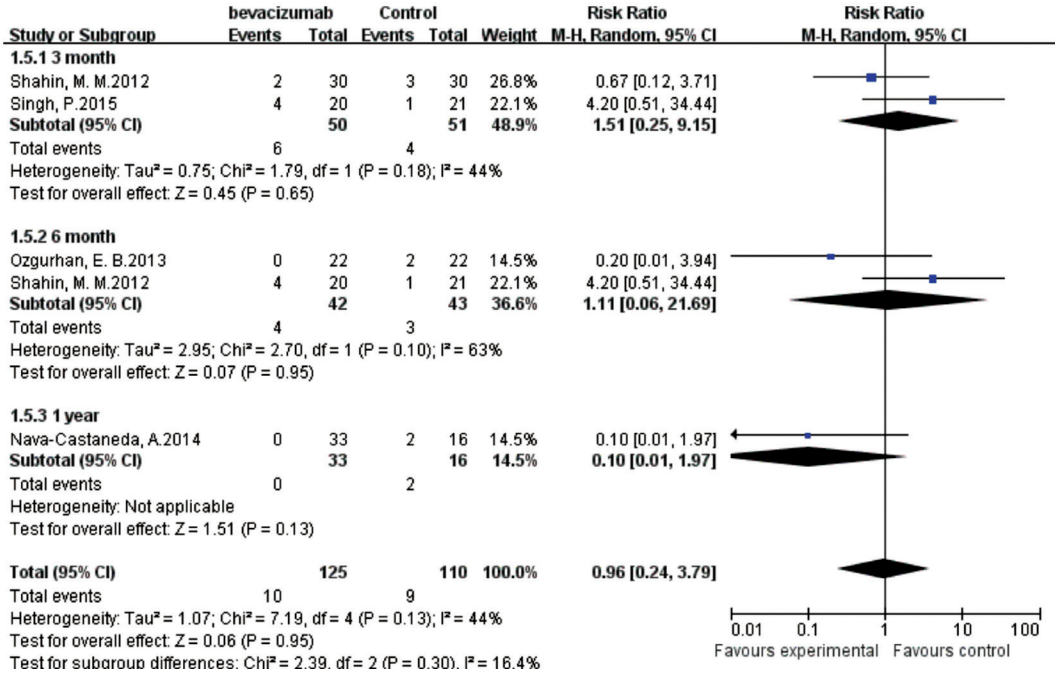

Figure 8 Forest plot for recurrence of patients with excision combined conjunctival autograft in bevacizumab group versus control group.

no intervention [3mo: 0.32 (0.05, 2.04), *P*=0.23; 6mo: 0.27 (0.05, 1.53), *P*=0.14; Figure 7] in simple excision subgroup. Similar outcome was observed in excision combined conjunctival autograft subgroup [3mo: 1.51 (0.25, 9.15), 6mo: 1.11 (0.06, 21.69); Figure 8].

DISCUSSION

Generally, pterygium recurrence rate rise along with the increases of follow-up period. It is more appropriate to analyze the recurrence for different follow-up period respectively. In our Meta-analysis above, no significant differences were found at 3mo and 6mo follow-up [3mo: RR=0.70 (0.34, 1.45); 6mo: RR=0.55 (0.23, 1.32)]. But at 1y follow-up, bevacizumab therapy seems to be effective in decreasing the recurrence rate [RR=0.14 (0.05, 0.36)]. However, the recurrence rate at 1y follow-up was genarated from only two studies with the small sample size. Furthermore, a number of factors such as route of administration, type of pterygium, surgical technique, age of patient and environmental agents may also have influence on pterygium recurrence. To avoid these confounding factors, we made the following subgroup analysis.

The routes of bevacizumab for pterygium therapy include topical application and subconjunctival application. Our Meta-analysis showed the recurrence rates were similar in patients with subconjunctival bevacizumab application or

not at 3mo and 6mo. Motarjemizadeh *et al*[21] shows a dose-response relationship between the different concentrations of bevacizumab eye drops and pterygium recurrence. Conversely, several studies didn't find the does-effect on recurrence[29]. To eliminate the potential influence of dosage, we analyzed the recurrence rate in patients with 1.25 mg/0.05 mL bevacizumab subconjunctival injection. No significant different recurrence rate was observed at 3mo and 6mo either. In 3 types of pterygium, impending recurrent pterygium is more likely to progress to a true recurrence, and a recurrent pterygium is more likely to have an exuberant fibrovascular growth response[30]. To exclude the potential influence of pterygium type, we analyzed the recurrence rate in patients with primary pterygium but found no significant difference between groups at 3mo and 6mo follow-up. Commonly used surgical techniques now contain bare sclera, excision with rotational conjunctival flap, and excision combined conjunctival autograft placement. The recurrence of pterygium is also affected by the surgical technique. To eliminate the influence of surgery technique, we analyzed the recurrence rate in patients with pterygium simple excision and excision with conjunctival autograft respectively. No difference between bevacizumab intervention versus placebo/no intervention was observed at 3mo and 6mo follow-up in both subgroups.

In some studies, bevacizumab had a role in decreasing grade, color intensity, size of pterygium. Wu *et al*[31] reported that the case treated with topical bevacizumab for 3wk produced prominent regression of limbal-conjunctival neovascularization and no recurrence of pterygium was noted at 6mo. Sarac *et al*[32] considered that average ocular irritation score, horizontal length, and the thickness of the pterygium could significantly decreased by intralesional bevacizumab (1.25 mg/0.05 mL) administration in 33 patients. A study conducted by Fallah *et al*[12] proved topical bevacizumab administration (5 mg/mL) could delay the recurrence of pterygium. However, in our analysis, we didn't observe the effect of bevacizumab in short term follow-up (3mo and 6mo). Razeghinejad *et al*[33] got a similar conclusion by a series of studies. At first, they used a single (1.25 mg) intraoperative subconjunctival bevacizumab administration and the outcome showed no difference at 6mo follow-up. Then, to investigate whether higher concentration of bevacizumab and more than one injection would have an effect, they compared the recurrence rate of patients with 7.5 mg bevacizumab, 2.5 mg bevacizumab, and balanced salt solution. However, no significant difference was observed as well[34]. They believed that the formation and recurrence of pterygium was related to several factors other than VEGF such as basic fibroblast growth factor (bFGF), transforming growth factor-beta (TGF-β), metal matrix proteinase-1 (MMP-1) and platelet derived growth factor[35]. So, simply block of VEGF may not enough.

To our knowledge, it is the first comprehensive review of the efficiency of bevacizumab therapy in pterygium treatment with different follow-up periods. Hu *et al*[36] performed an analysis about the effect of bevacizumab on pterygium. The study suggested topical or subconjunctival bevacizumab is relatively safe and well tolerated. To minimized potential selection biases and ensured accuracy of the abstracted data, we made analysis in patients with subconjunctival injection, primary pterygium, simple excision and excision with conjunctival autograft respectively. None of these analyses showed significant effect of bevacizumab in the decrease of recurrence rate. Considering the close relationship between recurrence and follow-up periods, we performed each analysis by different follow-up periods at different follow-up periods, but didn't find any obvious influence either. Nevertheless, our systematic review has several limitations. First, the number of included studies and participants in each subgroup analysis was relatively small. Second, the heterogeneity may be due to different type of pterygium, route of drug administration, surgeon's experience and other confounders. In order to get convinced results, more large scale of statistical data is needed.

In conclusion, the results of this Meta-analysis suggest that bevacizumab has no significant effect on the recurrence of pterygium in short term follow-up. Large scale RCTs and long-term follow-up are still needed.

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