• Meta-Analysis •

Laser therapy versus intravitreal injection of anti-VEGF agents in monotherapy of ROP: a Meta-analysis

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Abstract

● **AIM:** To compare the efficacy and safety between laser therapy and anti-vascular endothelial growth factor (VEGF) agents intravitreal injection monotherapy in type-1 retinopathy of prematurity (ROP) and aggressive posterior retinopathy of prematurity (APROP).

● **METHODS:** A systematic literature search was performed in PubMed, Cochrane Library, and Embase for original comparable studies. We included studies that compare laser therapy and intravitreal injections of anti-VEGF agents monotherapy in ROP regardless of languages and publication types.

● **RESULTS:** Complication incidence was significantly higher in laser therapy group (OR: 0.38; 95%CI: 0.19-0.75; *P*=0.005). Spherical equivalent (SE) was higher in laser therapy [weighted mean difference (WMD): 2.40, 95%CI: 0.88-3.93; *P*=0.002]. The time between treatment and retreatment was longer in laser therapy group (WMD: 8.45, 95%CI: 5.35-11.55; *P*<0.00001). Recurrence incidence (OR: 0.97; 95%CI: 0.45-2.09; *P*=0.93) and retreatment incidence (OR: 1.24; 95%CI: 0.56-2.73; *P*=0.59) were similar in two approaches. Subgroup analysis between type-1 ROP and APROP was not significant except SE reported in the included studies (*P*<0.0001).

● **CONCLUSION:** This Meta-analysis outcome indicates anti-VEGF agents are as effective as laser treatment, and safer than laser in type-1 ROP and APROP. The degree of myopia in APROP is higher than type-1 ROP. More randomized controlled trials in large sample size should be conducted in the future.

● **KEYWORDS:** anti-vascular endothelial growth factor; bevacizumab; laser therapy; Meta-analysis; retinopathy of prematurity; recurrence; ranibizumab

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INTRODUCTION

Retinopathy of prematurity (ROP) is an important cause of childhood blindness worldwide, and the incidence is rising[1]. It is caused by poor retinal vascular development[2]. High oxygen concentrations used or adjuvant oxygen therapy because of immature respiratory function have been considered to be the major risk factor for ROP[3-4]. Other risks for ROP include: gestational age (GA) and birth weight, medical conditions and treatments[5]. It encompasses a spectrum of pathologies that affect vision, from a mild disease that resolves spontaneously, to a severe disease that causes macular dragging or retinal detachment. Finally, it causes permanent visual loss[1,6]. There are approximately 50 000 children suffering from ROP per year globally and losing their sight for lacking a timely treatment[3]. However, it is a condition that can be successfully treated if it is discovered in a timely enough manner[7]. Over the past several decades, laser ablation, conventional treatment for ROP, which can inhibit the angiogenesis and decrease the possibility of progression of retinal detachment, has been regarded as the current standard treatment in ROP[3,8]. Meanwhile, we see some side effects of laser therapy including recurrence, retreatment, refractive error and visual field loss. As is known to all, vascular endothelial growth factor (VEGF) plays an essential role in angiogenesis[9] and it is justified to treat with an anti-VEGF agent in select cases[10], which makes researchers pay more and more attention to anti-VEGF agents to treat ROP. Nowadays, it is a new trend that VEGF inhibitors are applied to clinical treatment for ROP, such as bevacizumab and ranibizumab. However, the safety and efficacy of the two kinds of treatment remains uncertain.

As early as 2003, a study draws the conclusion that type-1 and threshold ROP are supposed to be treated[11]. Most of previous studies analyze type-1 and threshold ROP. Type-1 ROP is defined as zone I any stage with plus disease, zone I stage 3 with or without plus disease, or zone II stage 2 or 3 with plus disease[9]. Plus disease is defined as tortuosity and dilation of retinal vessels in the posterior pole of the eye and increase the risk of rapid adverse progression[4]. Threshold ROP is supposed to be present when stage 3 ROP is present in either zone I or zone II, with at least 5 continuous or 8 total clock hours of disease, and the presence of plus disease[12]. While comparisons between the two monotherapies are relatively lacking. The new trend is better than the conventional one? Can VEGF inhibitor take the place of laser therapy? How do we decide the clinical treatment of each type of ROP? The objective of this Meta-analysis is to compare the safety and efficacy between the two treatments in type-1 ROP and aggressive posterior retinopathy of prematurity (APROP). The comparison outcomes consist of recurrence incidence, complications incidence, retreatment incidence, spherical equivalent (SE), the time between treatment and retreatment. The eyes complications cover cataract, macular dragging, vitreous hemorrhage, retinal tears or detachment, *etc*.

MATERIALS AND METHODS

This systematic review and Meta-analysis performed coincides with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[13].

Evidence Acquisition A systematic literature search was performed in PubMed (1980 to December 7, 2018), Cochrane Library (1980 to November 4, 2018) and Embase (1980 to November 4, 2018) for original comparable studies without any restriction to languages. The following MeSH terms we search were “retinopathy of prematurity”, “laser therapy”, “intravitreal injections”, and “Bevacizumab”. The entry terms combined with MeSH terms were searched in [Title/Abstract]: “Prematurity Retinopathies”, “Prematurity Retinopathy”, “Retrolental Fibroplasia”, “ROP”, “Laser Therapies”, “Laser Ablation”, “Injection, Intravitreal”, “Avastin”, “anti VEGF”, *etc*. Relevant articles were searched and in the outcome list. We also searched the previous systematic review and Meta-analysis[14]. The latest day of literature search was performed on December 7, 2018. Meanwhile, a bibliographic database, EndNote X8, was used to filter duplicate articles[15].

Inclusion Criteria and Exclusion Criteria We two investigators (Wang SD and Zhang GM) extracted data independently from the retrieved studies including the assessment of quality. Any disagreement finally came to consensus by discussion. Data we collected are as follows: first author, year of publication, multicenter or single center study, study design, inclusion criteria and exclusion criteria, level of evidence, type of ROP, recurrence numbers, retreatment numbers, complication numbers, SE, and the time between treatment and retreatment.

Because there is a lack of randomized controlled trials (RCTs) studies relatively, all available RCTs and retrospective studies that compared intravitreal injections monotherapy of ranibizumab or bevacizumab with laser therapy in ROP were included. And the major parameters of comparison refer to recurrence incidence, retreatment incidence, complications numbers, SE at last follow-up, time between treatment and retreatment. Meanwhile, type of ROP can divide into two subgroups: type-1 ROP and APROP if there are enough data we can extract from the eligible studies.

Editorials, conference abstract, letters to the editor, non-comparative or nonrelevant comparison studies, review articles, case reports, notes, duplicate reports, nonrelevant topic, Meta-analysis, and animal experimental studies were excluded. And the studies whose patients are diagnosed as neither type-1 ROP nor APROP were also excluded.

Quality Assessment and Statistical Analysis In each study we evaluated the level of evidence in accordance with the criteria of the Centre for Evidence-Based Medicine in Oxford, UK[16]. The quality assessment of RCTs and retrospective studies was performed by Cochrane Risk of Bias Tool[17], and the modified Newcastle-Ottawa scale (NOS)[18], respectively. Generally, being equal or greater than 7 scores was deemed to be of high quality. RCTs were thought as high quality studies.

All the Meta-analysis was performed by using Review Manager version 5.3 (Cochrane Collaboration, Oxford, UK), and STATA SE version 12.0. The odds ratio (OR) was used to analyze dichotomous variables and the analysis of continuous variables used weighted mean difference (WMD). Such as, time between treatment and retreatment. The OR represents the odds of some adverse events occurring in the anti-VEGF monotherapy and laser therapy, such as recurrence incidence and complication incidence. Continuous data were presented as means and range values, the standard deviations (SD) were calculated using statistical algorithms[19-20].

We use a random-effected model for this Meta-analysis when there is heterogeneity between studies, which was assessed by the Chi-square test with significance set at P value less than 0.10, and the I^2 statistic. Otherwise, a fixed-effected model was reported[21]. Meanwhile, we drew forest plots to show variation and to explore heterogeneity. Begg’s test and funnel plot analysis were used to determine the presence of publication bias[20]. Studies which scores no less than 6 on the modified NOS were performed sensitivity analysis.

RESULTS

Of 337 potentially appropriate publications were identified and screened for retrieval by using the predefined search strategy. Of them 64 studies were duplications; 186 publications were

excluded after title and abstract review for conference abstract, case report, review, letters, editorial, note, Meta-analysis, animal study, topic not relevant and reply; 70 publications were excluded after full-text articles screening. Finally, there were 17 publications which fulfill the selection criteria included in the analysis. The search strategy was shown in the Figure 1. Four studies were RCTs[22-25], and thirteen studies were non-randomized comparable studies[2,12,26-36], including 12 retrospective design, and one study design unknown[31]. The characteristics of eligible studies including first author, year of publication, study design, single or multicenter study, level of evidence, sample size, recurrence number/incidence, retreatment number/incidence, complication number/incidence, matching, and quality scores for each study were shown in Table 1. Quality assessment of RCTs was shown in Figure 2. Analysis was done on 911 eyes in the anti-VEGF monotherapy group and 1924 eyes in the laser therapy group. Primary outcomes were shown in Table 2.

Pooling the data of eight studies, including seven type-1 ROP studies and one APROP, assessed the complication of anti-VEGF intravitreal injections monotherapy and laser therapy showed a significant difference favoring the laser group (OR: 0.38, 95%CI: 0.19-0.75, P=0.005; Figure 3) having higher complication incidence with moderate heterogeneity between studies (χ^2=12.15, df: 7, P=0.10, I^2=42%). The test of subgroup type 1 ROP and APROP showed no significant difference (χ^2=0.57, df: 1, P=0.45, I^2=0).

Ten studies assessed the SE reported in the included studies, and showed a statistically significant difference (WMD: 2.40, 95%CI: 0.88-3.93, P=0.002; Figure 4) favoring laser group having higher myopia with significant heterogeneity between studies (χ^2=142.55, df: 9, P<0.00001, I^2=94%). Meanwhile, the test of subgroup type 1 ROP and APROP showed a significant difference (χ^2=17.04, df: 1, P<0.0001, I^2=94.1%).

Recurrence data were available that investigated 2730 eyes across fifteen publications. Even though recurrence incidence were higher in the anti-VEGF group than the laser group, the assessment showed no statistically significant difference (OR: 0.97, 95%CI: 0.45-2.09, P=0.93; Figure 5) with significant heterogeneity between studies (χ^2=55.5, df: 14, P<0.00001, I^2=75%). The subgroup difference between type 1 ROP and APROP were not significant (χ^2=0.76, df: 1, P=0.38, I^2=0).

Retreatment data were reported in thirteen studies including eleven type 1 ROP and two APROP for 1455 eyes. The retreatment rate were higher in the laser group than in the anti-VEGF group, while the difference was not statistically significant (OR: 1.24, 95%CI: 0.56-2.73, P=0.59; Figure 6) with significant between-study heterogeneity (χ^2=40.39, df: 12, P<0.0001, I^2=70%). There was no significant difference

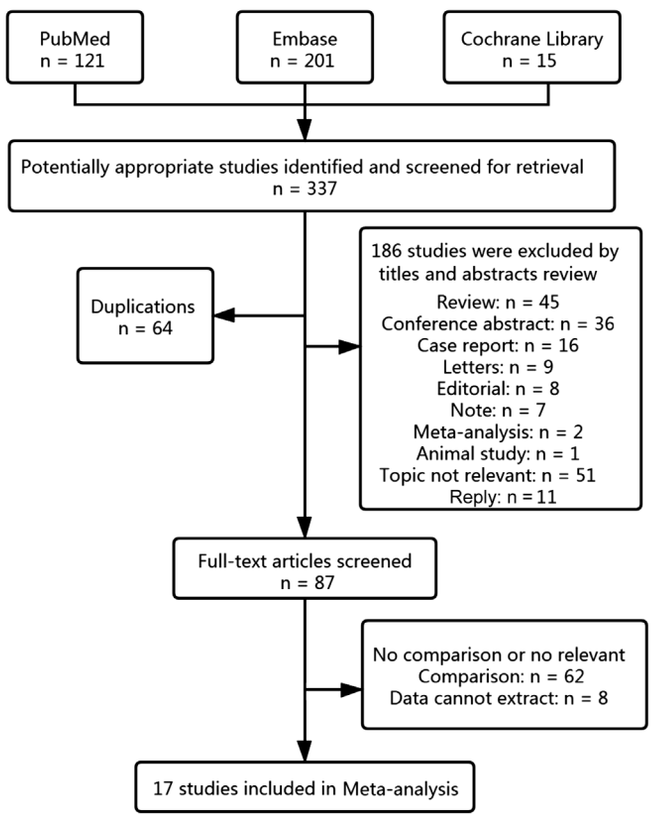

Figure 1 Search strategy.

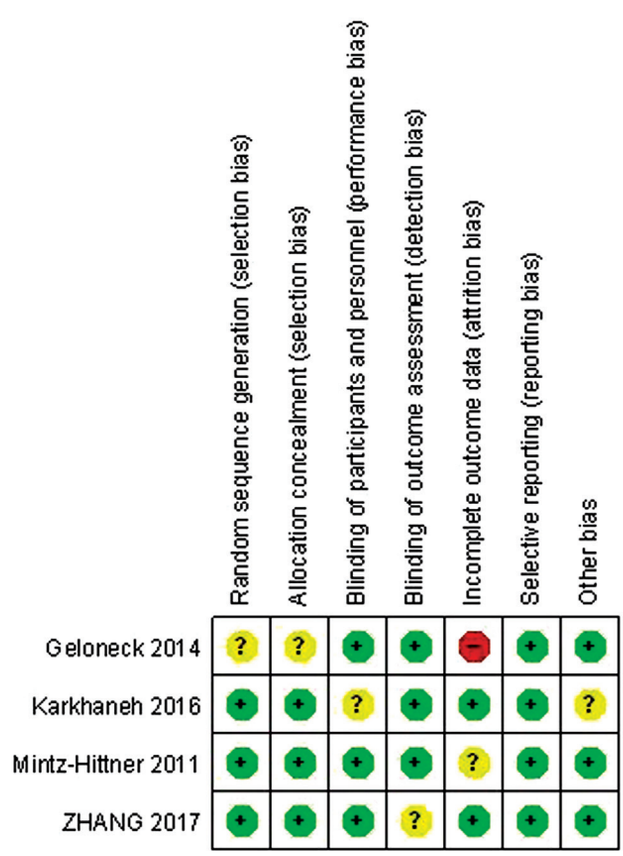

Figure 2 Quality assessment of randomized controlled trials For each quality domain, the proportions of included studies that suggest low, high, or unclear risk of bias and/or concerns regarding applicability are displayed in green, yellow, and red, respectively.

Table 1 Characteristics of included studies

First author, year	Design	Level of evidence	SC/MC	Eyes No.		Anti-VEGF therapy					Laser therapy				Time (wk)	Type	Matching criteria	Quality score
				anV	laser	Rec	Ret	Com	SE	Time (wk)	Rec	Ret	Com	SE				
Mintz-Hittner[22], 2011	RCT	2b	MC	140	146	6	NR	3	NR	16.0±4.6	32	NR	28	NR	6.2±5.7	Type 1	I, II, III, VI, VII, VIII	RCT
Spandau[26], 2013	r	3b	SC	8	8	4	4	NR	NR	NR	6	6	NR	NR	NR	APROP	I, II, V	6
Harder[12], 2013	r	3b	SC	23	26	0	0	0	-1.04±4.24	NR	1	1	1	-4.41±5.50	4	Type 1	I, II,	8
Geloneck[23], 2014	RCT	2b	MC	110	101	4	4	NR	-1.02±3.01	NR	17	17	NR	-6.73±6.59	NR	Type 1	I, II, V, VI	RCT
Kuo[30], 2015	r	3b	SC	15	14	NR	NR	NR	-1.53±2.20	NR	NR	NR	NR	-1.71±1.27	NR	Type 1	I, II, III, VI	6
Isaac[29], 2015	r	3b	SC	23	22	0	0	0	-3.57±6.19	NR	1	1	0	-6.39±4.41	NR	Type 1	I, II, III, V, VI	7
Hwang[28], 2015	r	4	MC	22	32	3	3	4	-2.4±3.5	9.0±5.7	1	1	9	-5.3±5.4	NR	Type 1	I, II, III, V, VI, VIII	6
Gunay[27], 2015	r	4	SC	48	30	6	6	0	0.42±3.42	NR	4	4	2	-6.66±4.96	NR	APROP	I, II, III, V, VI,	9
Walz[33], 2016	r	4	MC	38	132	8	8	NR	NR	10.4±8.57	21	21	NR	NR	3.8±1.57	Type 1	I, II, V	3
Nicoară[32], 2016	r	4	SC	34	12	5	3	NR	NR	NR	3	2	NR	NR	NR	APROP	I, II, III, V, VI, VII	8
Karkhaneh[24], 2016	RCT	2b	SC	86	72	9	9	0	NR	5.07±1.66	1	1	0	NR	3	Type 1	I, II, V, VI	RCT
Gunay[31], 2016	NR	4	NR	27	49	NR	NR	NR	0.25±1	NR	NR	NR	NR	0.75±0.69	NR	Type 1	III, VI,	5
Zhang[25], 2017	RCT	2b	SC	50	50	26	26	0	NR	12.62±7.93	2	2	0	NR	NR	Type 1	I, II, III, IV, VI, VII	RCT
Mueller[35], 2017	r	3b	NR	72	34	14	10	1	1±1.73	12.7±1.08	0	0	4	1.35±4.09	NR	Type 1	I, V, VI,	6
Kabataş[34], 2017	r	3b	SC	36	72	4	4	5	1.49±3.04	NR	10	10	12	-1.27±2.8	1.43	Type 1	III, VI	6
Morrison[2], 2018	r	3b	MC	26	963	0	NR	0	NR	NR	89	NR	25	NR	NR	Type 1	II, III,	3
Kang[36], 2019	r	4	SC	153	161	15	15	34	0.11±3.58	5.7	22	22	50	-1.09±3.68	2.3	Type 1	I, II, III, VI	7

NR: Not reported; RCT: Randomized controlled trial; r: Retrospective study; SC: Single center; MC: Multi center; anV: Anti-VEGF agents intravitreal injection monotherapy; Laser: Laser therapy; Rec: recurrence incidence; Ret: Retreatment incidence. Com: Complication incidence; SE: Spherical equivalent; Time: Time between treatment and retreatment; I: Birth weight. II: Gestational age; III: Gender; IV: Deliver methods; V: Postmenstrual age at treatment; VI: Same dosage of agents; VII: The proportion of single or twin births; VIII: Mother's race.

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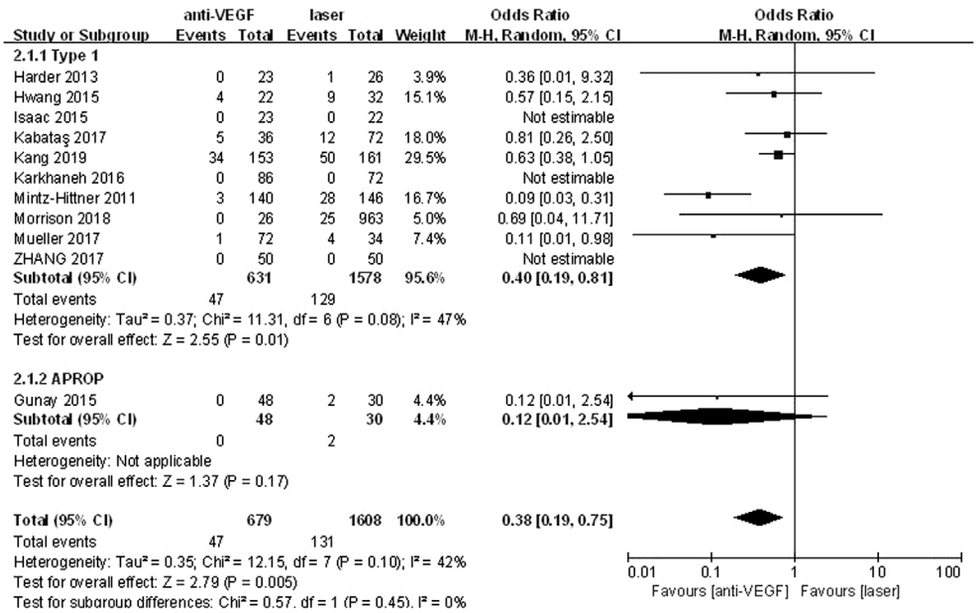

Figure 3 Complication comparison outcomes following laser therapy versus anti-VEGF agents intravitreal injection monotherapy for ROP.

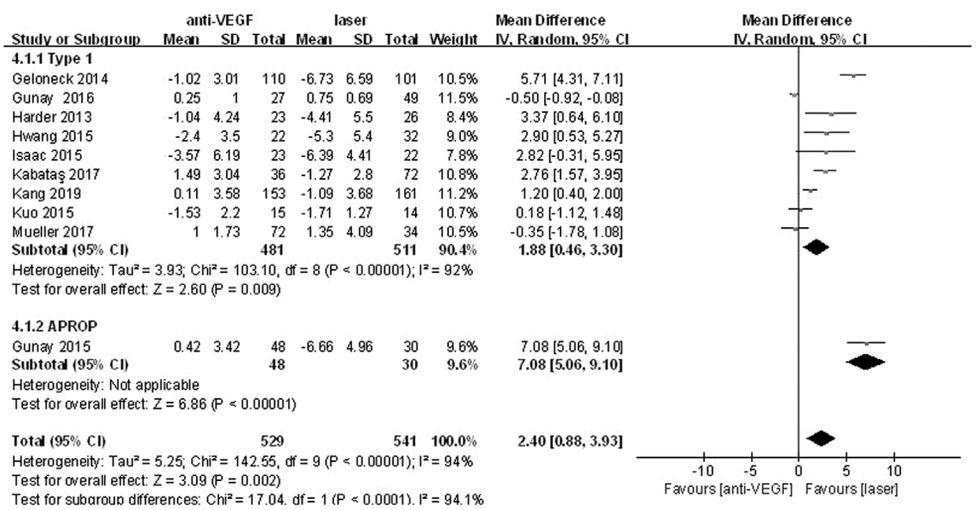

Figure 4 SE comparison outcomes following laser therapy versus anti-VEGF agents intravitreal injection monotherapy for ROP.

Table 2 Results of Meta-analysis comparison of laser therapy and anti-VEGF agents intravitreal injection monotherapy

Outcome of interest	Studies No.	Eyes No.		WMD/OR (95%CI)	*P*	Study heterogeneity			
		Anti-VEGF	Laser			χ^2	df	I^2	*P*
Recurrence incidence	15	869	1861	0.97 (0.45-2.09)	0.93	55.5	14	75%	<0.00001
Retreatment incidence	13	703	752	1.24 (0.56-2.73)	0.59	40.39	12	70%	<0.0001
Complication incidence	11	679	1608	0.38 (0.19-0.75)	0.005	12.15	7	42%	0.1
SE	10	529	541	2.40 (0.88-3.93)	0.002	142.55	9	94%	<0.00001
Time between treatment and retreatment	2	178	278	8.45 (5.35-11.55)	<0.00001	4.40	1	77%	0.04

VEGF: Vascular endothelial growth factor; WMD: Weighted mean difference.

between subgroup type 1 ROP and APROP (χ^2=1.75, df: 1, *P*=0.19, I^2=42.7%).

Data on the time between treatment and retreatment were extracted from two studies. The time was significantly longer in laser group (WMD: 8.45; 95%CI: 5.35-11.55, *P*<0.00001; Figure 7) with high heterogeneity between studies (χ^2=4.40, df: 1, *P*=0.04, I^2=77%).

Ten studies[12,26-30,32,34-36] which scored no less than 6 on the modified NOS and the four RCTs[22-25] were conducted the sensitivity analysis[37] (Table 3). No significant change was observed in any of the outcomes. The heterogeneity between studies remained significant in recurrence incidence, retreatment incidence, and SE. And it increased significantly in complication incidence. There was only one study left

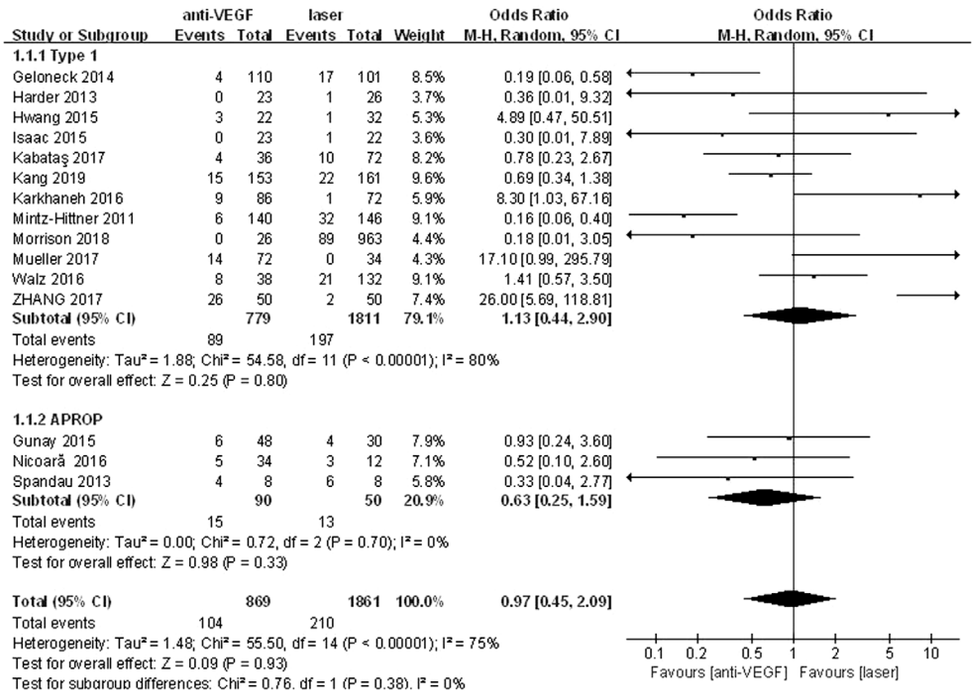

Figure 5 Recurrence comparison outcomes following laser therapy versus anti-VEGF agents intravitreal injection monotherapy for ROP.

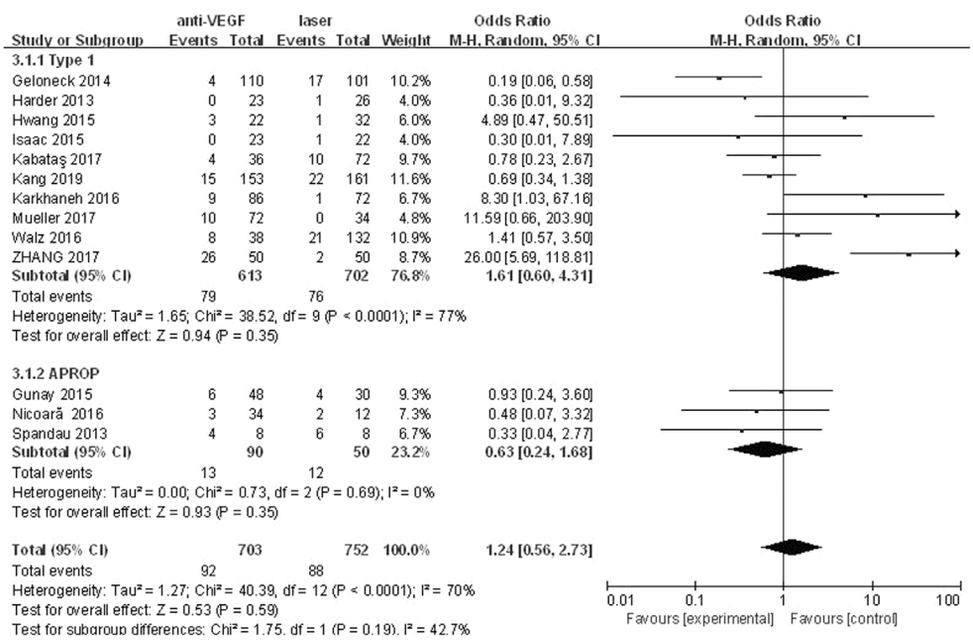

Figure 6 Retreatment incidence comparison outcomes following laser therapy versus anti-VEGF agents intravitreal injection monotherapy for ROP.

which reported time between treatment and retreatment and scored 6 or more, so the between-study heterogeneity was not applicable.

Figure 8 shows a Begg's funnel plot of the publications included in this Meta-analysis that reported recurrence incidence. We can see 5 studies lie outside the 95%CIs, with most studies lie inside the vertical, indicating no obvious publication bias (*P*=0.237).

DISCUSSION

This Meta-analysis including 2835 eyes totally comparing the efficacy of anti-VEGF intravitreal injections monotherapy and laser therapy for ROP showed no overall difference on recurrence outcome and retreatment outcome, which means anti-VEGF monotherapy and laser therapy for ROP have similar therapeutic efficacy. While the laser group suffered more from complication incidence and myopia for higher possibility than anti-VEGF group, which showed anti-VEGF monotherapy for either type 1 ROP or APROP was safer than laser therapy. The laser treatment may play a part by leading to involution of pathological vessels and restraining the

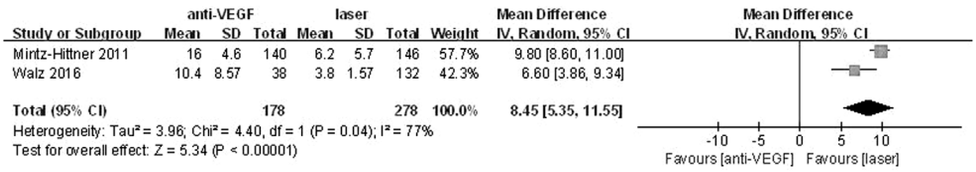

Figure 7 Time between treatment and retreatment outcomes following laser therapy versus anti-VEGF agents intravitreal injection monotherapy for ROP.

Table 3 Sensitivity analysis comparing laser therapy and anti-VEGF agents intravitreal injection monotherapy

Outcome of interest	Studies No.	Eyes No.		WMD/OR (95%CI)	*P*	Study heterogeneity			
		Anti-VEGF	Laser			χ^2	df	I^2	*P*
Recurrence incidence	13	805	766	1.29 (0.51, 3.28)	0.59	56.69	12	79%	<0.00001
Retreatment incidence	12	665	620	1.24 (0.50, 3.07)	0.65	40.1	11	73%	<0.0001
Complication incidence	10	653	645	0.36 (0.17, 0.75)	0.007	12.09	6	50%	0.06
SE	9	504	492	2.77 (1.21, 4.34)	0.0005	76.24	8	90%	<0.00001
Time between treatment and retreatment	1	140	160	9.91 (8.55, 11.27)	<0.00001	Not applicable			

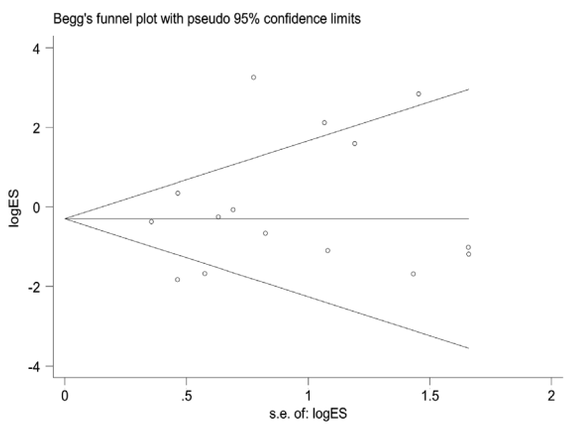

Figure 8 Beggs's funnel plot for assessing publication bias.

development of retinal detachment. However, this coagulation of the avascular retina is a destructive therapy and does not ameliorate retinal development[38]. Moreover, the time between treatment and retreatment was longer in laser therapy than in anti-VEGF intravitreal injections monotherapy. It indicated that laser therapy could inhibit the angiogenesis for a longer time. The significant difference between type-1 ROP and APROP in terms of SE reported in the included studies demonstrated different types of ROP, different degrees of myopia. Even though laser therapy for ROP was regard as golden standard for its therapeutic efficiency, the complication incidence and postoperative myopia were supposed to be attached great importance to its side effects.

When it came to some new approaches to treat diseases, the most concerns we paid were not only its efficacy, but also its security. Following the publication of the BEAT-ROP study in 2011, bevacizumab injection therapy was regarded as a possible alternative to laser for treatment-requiring diseases in zone I and posterior zone II[29]. The duration of anti-VEGF agents applied in clinic was not long. Even if anti-VEGF agents became more and more prevalent, the efficiency and safety would remain uncertain in the long term. This Meta-analysis might help some oculists give more appropriate therapies for children who suffered from treatment-requiring ROP.

The present Meta-analysis includes some limitations as follows. First of all, in the final included publications, with only four exceptions, which was a randomized controlled trials with small sample size, 12 studies were retrospective and one study design was unknown. The researches were performed with different levels of surgical expertise. Ten studies included were carried out in single clinical center and five were conducted in multi-center and two were unknown. A lack of random sequence generation and blinding could increase the risk of bias. More and more RCTs were supposed to be large-scale in the future. Second, different ophthalmologists that performed the two approaches have different experiences, which would influence the results to a certain extent. Operators who lack experience would increase the length of time of retreatment. In one study, different dosages of bevacizumab were used in anti-VEGF group because the injection was performed by different surgeons[12]. Third, follow-up time was not adequate. Nine included studies did not mention or compare the follow-up time and most of the rest studies reported the follow-up time for less than twelve months. A long-term follow-up over twelve months was recommended in the future researches in case we would miss the recurrence and then would not be able to conduct a prompt retreatment. In addition, some data such as the time between treatment and retreatment, and SE were not be retrieved from most included studies and recurrence incidence, retreatment incidence and

complication incidence were not recorded in several studies, which decreased the sample size and could increase the risk of bias. Finally, the heterogeneity of the recurrence incidence, retreatment incidence, SE and the time between treatment and retreatment has been shown to be significant. High heterogeneity could decrease the credibility of evidence. A random-effected model was used for this Meta-analysis when *P* value was less than 0.1. We could observe the heterogeneity decreased but the significance remained unchanged. Different studies had different definitions in terms of recurrence and complication. Recurrence was defined as recurrent plus disease, recurrent neovascularization, or progression of traction in spite of treatment[28], and progressing extra-retinal proliferation (stage III ROP) of at least 3 clock hours with the potential to exert traction on the retina[35]. In most included studies, vitreous hemorrhage was considered as a complication except one for vitreous hemorrhage can relate to treatments or disease progression[2]. One study[36] defined the complications including death and strabismus requiring operation while most of other studies did not include this. Different dosages and different agents had different outcomes. One study drew a conclusion that a single intravitreal dose of 0.2 mg ranibizumab showed favorable anatomical and functional outcomes in eyes with type-1 ROP[39]. And one conference abstract indicated that intravitreal injection of bevacizumab at lower dosage (0.25 mg) had similar efficacy as 0.625 mg dosage but with significantly lower systemic exposure[40]. One article discussed that bevacizumab is the most commonly used anti-VEGF agent in ROP, but ranibizumab had a shorter half-life with the potential for decreased systemic toxicity[10]. The incidence of disease relapse was higher in eyes which received ranibizumab[41]. Perhaps it contributed to the heterogeneity of recurrence and retreatment. In addition, different dosages of bevacizumab injection, sample size, experienced surgeons, different types of ROP, different zones of ROP, and other factors among the studies might account for the high heterogeneity.

Nevertheless, this Meta-analysis was meaningful to perform because there is rarely Meta-analysis about the comparison between anti-VEGF monotherapy and laser therapy for ROP. These two approaches were controversial in clinical application. Compared to the previous analysis[14], both of them analyzed the anti-VEGF agents monotherapy and laser therapy. Not only did this Meta-analysis conduct literature search in more databases, but also more RCTs and retrospective studies were included in this Meta-analysis. Conference abstract and letters were included in previous analysis but excluded in this analysis, thus the evidence was relatively reliable. We extracted data and analyzed data in accordance with the demand of the methods of Meta-analysis and formulated the strict criteria to include and exclude publications. Therefore, to some extent, this Meta-analysis provided an up-to-date guidance in treatment of ROP for ophthalmic surgeons.

This Meta-analysis outcome indicated anti-VEGF agents were as effective as laser treatment and safer than laser therapy in type-1 ROP and APROP. The two approaches appear to be similar in recurrence and retreatment. Laser therapy may be associated with a higher myopia and more complications. Myopia in APROP was higher than type-1 ROP. More RCTs in large sample size should be conducted in the future.

Through literature search in online databases, we compared the laser therapy and intravitreal injection of ranibizumab or bevacizumab for ROP in recurrence incidence, retreatment incidence, complication incidence, time between treatment and retreatment, and SE. We found the two approaches has similar efficacy and anti-VEGF agents injection monotherapy is safer.

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