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Refractive Outcomes After Intravitreal Anti-vascular Endothelial Growth Factor (Anti-VEGF) Versus Laser Photocoagulation for Retinopathy of Prematurity: A meta-analysis

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Key words: Retinopathy of Prematurity; Anti-VEGF; Refractive Errors; myopia

Abstract

Objective: To evaluate the effect of intraocular injection of anti-vascular endothelial growth factor (anti-VEGF) on the refractive status of premature infants with retinopathy.

Design:Systematic review and meta-analysis to evaluate the refractive status of anti-VEGF in Retinopathy of prematurity(ROP) children.

Methods: We searched four databases through January 2020, including PubMed, Web of Science, EMBASE, and ClinicalTrials.gov website, to identify randomized, controlled, and observational studies that investigated refractive errors between anti-VEGF and laser therapy. We used a random-effects model to pool outcomes. The outcome measures were spherical equivalent(SE), axial length (AL), anterior chamber depth (ACD), and lens thickness (LT).

Results: Thirteen studies with 1850 eyes were assessed, of which 914 eyes were in anti-VEGF group, while 936 were in control (laser) group. Children who received anti-VEGF treatment had less myopia than those who received laser therapy (Mean Difference 1.80, 95% CI: 0.97 to 2.63, P < 0.0001 , I^2 = 78%). axial length (Mean Difference-0.04, 95% CI: -0.30 to 0.21,P=0.75,I^2 = 30%) , anterior chamber depth (Mean Difference 0.19, 95% CI: -0.14 to 0.52,P=0.25,I^2 = 85%) and lens thickness (Mean Difference 0.06; 95% CI: -0.56 to 0.67, P =0.85,I^2 = 97%) had no statistical significance on anti-VEGF therapy for retinopathy of prematurity.

Conclusions*:* Our meta-analysis indicates that anti-VEGF therapy reduces

myopia compared to laser therapy. However, the number of published articles on refractive error in ROP is limited. Hence, it is necessary to conduct high-quality and powerful randomized controlled trials in the future.

PROSPERO registration number: CRD42020160673

Strengths and limitations of this study

Our meta-analysis adhered to the methodology recommendations of the Cochrane handbook. we conducted a thorough literature search.

The article has a formal registered review protocol on PROSPERO, and our article was conducted and reported with rigorous methods following the PRISMA.

We included other parameters that may affect the refractive errors of ROP children, such as ACD, LT, AL, in our meta-analysis.

Most of the literature we included are observational studies, and only 2 articles are RCTs, if more RCTs are included, we can draw more reliable conclusions.

Introduction

Retinopathy of prematurity (ROP) is a common cause of blindness in developed countries and is increasingly prevalent in developing countries.[1] Characterized by retinal ischemia, aberrant angiogenesis, fibrovascular proliferation, and progressive vitreoretinal traction, ROP accounts for 14% of childhood blindness within the United States and greater than 20% in developing countries.[2]

Retinopathy of prematurity is a unique retinal vascular proliferative disease occurring in premature infants and low birth weight infants.[3] Normally, retinal

vascularization occurs around 12 weeks and is completed in 36 to 40 weeks of gestation. Because premature infants leave the uterus prematurely, the retinal system is immature. The loss of maternal interaction environment and exposure to high oxygen in premature infants can lead to the cessation of retinal vascularization, damage to capillary endothelium, hypoxia of the retinal blood vessels, stimulation of fibrovascular tissue proliferation, and finally may lead to traction retinal detachment.[4]

In the past, laser photocoagulation has been the main treatment for ROP. In spite of the effectivity and safety provided by laser photocoagulation, a few defects still remain in this kind of treatment, such as high myopia, visual field loss, and retinal destruction. With the intensive study of ROP, it was found that the levels of VEGF in the vitreous of eyes at stage 4 ROP have greatly increased.[5] In a normally developing retina, VEGF promotes the development of blood vessels from the optic nerve to the periphery, but in preterm infants, the overexpression of VEGF leads to abnormal vascular proliferation.[6] Therefore, researchers have sought to use anti-VEGF to treat ROP. Many studies have shown that intravitreal injection of anti-VEGF drugs may be an effective intervention measure when used in the clinical treatment of ROP.[7, 8 9] However, intravitreal injection of anti-VEGF drugs for the treatment of ROP is a relatively short-term clinical application, and its long-term complications are unclear. There is still controversy as to whether or not postoperative refractive errors can be caused. Kang et al's study[10] showed that anti-VEGF drugs do

not cause refractive error after ROP treatment, while Kabatas et al[11] found that intravitreal injection of anti-VEGF drugs treatment is the same as laser photocoagulation treatment, both can cause refractive errors, and there is no statistical difference between the two groups.

With the increasing clinical application of anti-VEGF drugs, it is urgent to know whether these drugs can also cause refractive errors in children with ROP. Hence, the purpose of our meta-analysis is to evaluate the effect of anti-VEGF drugs on the refractive status of ROP compared to laser treatment and to further verify the clinical safety of anti-VEGF drugs. The outcome measures are spherical equivalent (SE), axial length (AL), anterior chamber depth (ACD) lens thickness (LT).

Methods

We report our study according to the meta-analyses of PRISMA guidelines.[12] Our study has been registered on PROSPERO (number CRD42020160673).

Data sources and search strategy.

From inception to January 2020, We searched PubMed, Web of Science, EMBASE, and ClinicalTrials.gov website using keywords and medical subject headings. Only studies published in the English language were considered for inclusion. Additionally, we searched the reference lists of included studies to prevent missing some potentially available articles. Search terms included "Retinopathy of Prematurity," "Prematurity Retinopathy," "Retrolental

Fibroplasia," "Fibroplasia, Retrolental," "ROP," "Anti-VEGF," "Bevacizumab," "Avastin," "Lucentis," "Ranibizumab," "aflibercept," "Anti-vascular endothelial growth factor," "Mvasi," and "Refractive Errors," "Disorders, Refractive," and "Ametropias." The search strategy is detailed in the S1 strategy(online supplementary material).

Study selection and eligibility criteria.

Each study was independently screened by two authors (QHK and MXS). Discrepancies between the screenings of the two reviewers were solved through discussion with the third author (WM). The inclusion criteria in our article were following: 1) Study population: Children who have been clearly diagnosed with retinopathy of prematurity; 2) Intervention group: Intraocular injection of anti-VEGF, including any anti-VEGF drug that can be used in children with ROP ;3) Control group: Laser treatment of the eye included retinal argon laser and diode laser.; 4)Outcome of interest: The refractive status of treated ROP children, including spherical equivalent (SE) and some ocular biometric structural features, such as axial length (AL), anterior chamber depth (ACD), and lens thickness (LT); 5) Study design: Randomized controlled study and observational study. We excluded children with stage 4 or 5 ROP or other eye diseases (such as congenital cataract or glaucoma) prior to treatment.

Data extraction and quality assessment.

The following information was extracted from the included studies: the name of

the first author, publication year, sample size, number of eyes, GA (gestational age), BW (birth weight), follow-up time, the type of anti-VEGF, anti-VEGF dose, and result data (SE, AL, ACD, LT). When two anti-VEGF drugs were included in the literature, we extracted the data separately and compared the data with the control group. We entered the extracted data into an Excel file. Two of the authors (QHK and MXS) assessed the quality of studies by the Newcastle-Ottawa Scales.[13] The NOS consists of 4 items for subject selection (4 points), 1 item for comparability between groups (2 points), and 3 items for outcome measurement (3 points). Studies of different quality are awarded different scores, with a maximum of 9, a moderate quality of 4–6, and a high quality of 7–9.[14]

Statistical analysis.

The weighted mean differences (WMDs) with 95% CIs of continuous variables were calculated. Meanwhile, heterogeneity between included studies was discussed using the I^2 statistic. I^2 values of 25% to 50%, 50% to 75%,75% to 100% were considered low heterogeneity , moderate heterogeneity and high heterogeneity.[15] Because of the potential for heterogeneity between studies, we used a more conservative version of the random-effects model. To evaluate potential publication bias, we used a visual funnel plot. If the funnel plot was asymmetric, there was publication bias. Meanwhile, the Egger test was also used to provide an accurate assessment, whereby if $p < 0.05$, it was considered

statistically significant, i.e. there was some degree of publication bias. All statistical analyses were performed using RevMan software (version 5.3, Nordic Cochrane Centre) and Stata software (version 12.0, Stata Corp LP).

Results

Literature search.

The initial search identified 121 records. After screening the titles and abstracts, 31 potentially eligible studies were assessed for inclusion. After reading the full text in our meta-analysis, a total of 13 studies were finally included. The study selection diagram is presented in **Figure 1**.

A total of 13 studies were selected, including 2 RCTs[16, 17] and 11 observational studies[11, 18-27]. According to the scoring criteria of the Newcastle-Ottawa scale, eleven studies were evaluated as high quality, and two studies were evaluated as moderate-quality. The median NOS score of the included studies was 8 (range of 6-8). These studies were published between 2013 and 2019. The sample size of the studies ranged from 12 to 397, with a total of 1850 eyes comprising 914 in the anti-VEGF group and 936 in the control group. In the anti-VEGF group, anti-VEGF drugs were bevacizumab and ranibizumab. Only one of the above-mentioned drugs was used in 12 pieces of literature and two drugs were used in one literature. The dosage of anti-VEGF drugs also varied in all the included literature. The minimum dose was 0.2mg, the maximum dose was 1.25mg, and the majority of the literature used 0.625 mg. After injection of anti-VEGF drugs, ROP children were followed regularly for more than 6 months,

ranging from 9 months to 5 years. Among the thirteen studies included here, all reported spherical equivalent, four reported axial length, three reported anterior chamber depth, and two reported lens thickness. We presented the main information within the included studies in our meta-analysis (**Table 1**)

Table 1: Main Characteristics of Studies Included in the Meta-analysis

First author/year	region	Group	patients /eyes(n)	GA(weeks) (mean±SD)	BW(g) (mean±SD)	Follow-up (months)	Type of Anti-VEGF	Anti-VEGF dose(mg)	NOS score
Harder et al[18]	Germany	Anti-VEGF laser	12/23 13/26	25.20 ± 1.60 25.30± 1.80	622.00 ± 153.00 717.00 ± 197.00	12	bevacizumab	0.375 or 0.625	7
Hwang et al[19]	American	Anti-VEGF laser	11/22 17/32	NA	668.10 ± 127.30 701.40 ± 118.80	21.7 32.5	bevacizumab	0.625	8
Kabataş et al[11] ⋆	Turkey	Anti-VEGF laser	12/24 36/72	26.10 ± 2.27 27.70 ± 2.70	841.00 ± 235.00 1,112.00 ± 362.00	18	bevacizumab	0.625	8
Kabataş et al[11] ⋆	Turkey	Anti-VEGF laser	6/12 36/72	26.00 ± 1.26 27.70 ± 2.70	840.00 ± 177.00 1,112.00 ± 362.00	18	ranibizumab	0.25	8
Kuo et al[20]	Taiwan	Anti-VEGF laser	15/15 14/14	27.33 ± 2.94 27.43± 2.93	1,079.67 ± 357.48 1,006.79 ± 327.65	3 years of age	bevacizumab	0.5	7
Kang et al[21]	Korea	Anti-VEGF laser	12/22 15/30	27.40 ± 2.00 34.00 ± 2.90	983.20 ± 265.60 961.00 ± 286.50	4 years of age	bevacizumab ranibizumab	0.625 0.2	7
Isaac et al[22]	Canada	Anti-VEGF laser	13/23 12/22	25.20 ± 1.40 25.00 ± 1.10	722.00 ± 131.00 674.00 ± 175.00	16.00±6.00 6.00±3.00	bevacizumab	0.625	8
Vujanović et al[23]	Serbia	Anti-VEGF laser	21/42 45/90	29.00 ± 4.00 30.00 ± 4.00	1,175.00 ± 425.00 1,200.00 ± 500.00	9	bevacizumab	0.625	8

Table 1 *(continued)*

First author/year	region	Group	patients /eyes(n)	GA(weeks) (mean±SD)	BW(g) (mean±SD)	Follow-up (months)	Type of Anti-VEGF	Anti-VEGF dose(mg)	NOS score
Gunay et al[24] ⋆	Turkey	Anti-VEGF laser	55/107 57/113	27.31 ± 2.18 28.23 ± 2.50	1005.29 ±411.19 1119.47 ± 336.96	19.40±6.43 20.68±6.89	bevacizumab	0.625	8
Gunay et al[24] ⋆	Turkey	Anti-VEGF laser	22/44 57/113	27.95 ± 2.90 28.23 ± 2.50	1195.90 ± 466.98 1119.47 ± 336.96	18.96±4.79 20.68±6.89	ranibizumab	0.25	8
Chen et al[25]	Taiwan	Anti-VEGF laser	13/25 12/22	26.46 ±1.51 25.50 ±1.24	862.54 ±197.65 815.83 ±151.07	NA	bevacizumab	0.625	7
Lee et al[26]	Taiwan	Anti-VEGF laser	17/33 13/24	26.60 ± 1.60 26.60 ± 2.50	874.10 ± 228.70 803.10 ± 144.90	> 48	bevacizumab	0.625	6
Roohipoor et al[27]	Iran	Anti-VEGF laser	NA/397 NA/190	27.8	1146	> 12	bevacizumab	0.625	8
Geloneck et al[16]*	American	Anti-VEGF laser	56/110 53/101	24.3	625	2.5 years of age	bevacizumab	0.625	8
O'Keeffe et al[17] *	Irish	Anti-VEGF laser	15/15 15/15	25±1.25	780±135	60	bevacizumab	1.25	6

***:** RCT, Randomized Controlled Trial; NOS: Newcastle-Ottawa Scale; NA: not applicable; GA: gestational age; BW: birth weight;

⋆ : There are two types of Anti-VEGF drugs included in the literature, so the details are listed separately

Main outcomes

Spherical equivalent (SE). Thirteen studies reported the spherical equivalent (SE), with 914 eyes in the anti-VEGF group versus 936 eyes in the control group. (**Figure 2**). The anti-VEGF group had a higher spherical equivalent (MD 1.80, 95% CI: 0.97 to 2.63). compared to the control group, with high heterogeneity (I^2 = 78%). The findings of the subgroup analysis for the spherical equivalent according to type of article included are summarized in **Figure 3.**

Axial length (AL). Four studies[23, 25, 26] reported the axial length (AL), with 251 eyes in the anti-VEGF group versus 362 eyes in the control group. (**Figure 4**). There was no statistical difference between the groups (MD -0.04, 95% CI: -0.30 to 0.21), with low heterogeneity (I^2 = 30%).

Anterior chamber depth (ACD). Three studies[23, 25, 26] reported anterior chamber depth (ACD) in ROP children with or without anti-VEGF. Our study found no difference between anti-VEGF and the control group(MD 0.19; 95% CI: -0.14 to 0.52, I^2 = 85%).(**Figure 5**) There was a high heterogeneity(I^2 = 85%).However, in sensitivity analysis by excluding Vujanović's study, moderate heterogeneity can be observed(MD 0.39; 95% CI: -0.06 to 0.84, I^2 = 64%).

Lens thickness (LT). Two studies[23, 25] assessed lens thickness(LT) on anti-VEGF group and a control group. The difference of LT between anti-VEGF and laser group had no significant difference (MD 0.06; 95% CI: -0.56 to 0.67, P =0.85), and the I^2 was 97%. (online supplementary material S2 forest plot).

Publication Bias

To investigate the publication bias, we made a funnel plot using Stata software. Through visual examination and statistical calculations, we did not find the existence of any publication bias (P =0.401 by Egger test). (online supplementary material S3 funnel plot)

Discussion

Our meta-analysis identified 13 studies investigating the association between the treatment groups and refractive errors for ROP. The analysis of this study was based on SE, AL, ACD, and LT. As the results showed, there was a statistically significant difference in SE between the two groups. In other words, anti-VEGF treatment reduces myopia in ROP children compared to laser treatment, and this evidence is consistent in both the comprehensive and subgroup analyses. However, no statistical significance was found in other variables in our study.

A meta-analysis has been published on similar subjects.[28] Tan et al.'s meta-analysis included a total of 7 articles, including a total of 519 eyes. The anti-VEGF drug was limited to bevacizumab. Although the main finding of our meta-analysis was consistent with previous meta-analyses, there are some differences between them. Firstly, our literature included 13 articles with a total of 1850 eyes. Our current article is the latest meta-analysis, which includes some recently published literature, and further strengthens the results of the previous meta-analysis by increasing the statistical power of the number of cases. secondly, We increased the variety of anti-VEGF drugs, not only limited

to bevacizumab, but also other commonly used anti-VEGF drugs in clinical practice, such as ranibizumab. This can bring the conclusion closer to clinical reality. Lastly, we added other ocular parameters to investigate the association with refractive errors between anti-VEGF drugs and laser therapy, such as ACD, LT, AL. A previous study has shown that ocular refractive parameters including ACD, LT, AL may be related to myopic adults with ROP,[29] but there is no evidence that laser treatment and anti-VEGF treatment have different refractive statuses in ROP children. Therefore, we analyzed the above ocular parameters in laser and anti-VEGF groups. This further increases the evidence that anti-VEGF treatment is safe for ROP children.

This is a meta-analysis of 13 papers synthesizing the literature to evaluate the refractive safety of anti-VEGF for children with ROP. Our meta-analysis shows that anti-VEGF treatment has better refractive results compared to laser treatment. As seen in previous studies, anti-VEGF therapy reduces myopic more than the laser treatment in the current study. Describing refractive errors usually use SE in most previously published studies, the spherical equivalent is considered the primary measure of refractive error .so we also used the parameter to explore the differences between the two groups in our article. Kuo et al[20] and Issec et al[22] reported no statistical difference in refractive error between anti-VEGF and laser groups. However, our meta-analysis found that anti-VEGF therapy reduces myopia and refractive errors more, compared to laser treatment. Two factors may explain the difference. First, both articles

utilized a small sample size for their research. Second, the children included had a higher proportion of severe ROP. Therefore, anti-VEGF therapy may be an alternative to laser therapy in reducing refractive error in ROP children. Our subgroup analysis found that anti-VEGF therapy had a better refractive effect than laser therapy, whether in RCTs or in observational studies. Although laser therapy has been considered the first choice of ROP treatment and is well-established in terms of safety and efficacy, the retina is permanently cauterized, resulting in inadequate vascularization and the risk of visual field loss, high myopia, and cataracts. In refraction, there is also an article suggesting that laser treatment may be a risk factor for refractive error in children with ROP[30] Therefore, when treating ROP, we have to consider the impact of the damage that may result from laser treatment on the ROP children's future refractive status, and it is necessary to find a treatment method that increases both effectiveness and safety.With the in-depth study of the ROP mechanism by researchers, it was found that intraocular injection of anti-VEGF may be a good alternative to laser treatment.[22] Intraocular injection of anti-VEGF drugs has the advantage of small trauma, less pain, and easy operation, and it is increasingly used by a wide number of clinicians. Hence, it is essential to clarify the safety of refractive aspect as soon as possible, and our meta-analysis provides good evidence for anti-VEGF drugs in terms of refractive safety. Changes in the biometric structure of the eye, such as ACD, LT, AL corneal curvature and corneal diameter may be related to an increased refractive error in previously

published literature.[31-33] We, therefore, consider the above indicators of ocular biometric structure to be essential when verifying the refractive status of children with ROP. Although previous meta-analyses have reported refractive outcomes after treatment of ROP with anti-VEGF therapy, these meta-analyses have not explored the relationship between refractive outcomes and biometric structure of the eye when comparing anti-VEGF and laser therapy. Hence, our article further investigated these parameters between the two groups. However, our study shows that these parameters have no statistically significant difference when comparing the anti-VEGF and laser group. But there is also much debate about whether anti-VEGF treatment of ROP will cause changes in ocular parameters. Lee et al found that AL did not differ among different treatment groups. Gunay et al[34] reported that in children who receive anti-VEGF therapy, the axial length axial might be related to the development of myopia and not related to anterior chamber depth or lens thickness. The BEAT-ROP believes that anti-VEGF treatment may continue the local growth factor expression and signaling pathways, allowing the anterior segment to develop normally[16]. The small number of articles that include ocular biometric structure makes it difficult to draw definitive conclusions, so we need more high-quality RCTs to verify the impact of anti-VEGF on the ocular biometric structure in the future. For future research, we believe that we should focus on the following two aspects. Firstly, there is no unified standard for the dose used in the treatment of ROP with anti-VEGF. Most clinical applications used doses are

half of the adults, but if other doses of anti-VEGF treatment of ROP affect the result, we do not know, so in the future, a clear plan for the dose of anti-VEGF needs to be proposed. Secondly, there is no clear standard for the follow-up time of children with ROP. If the follow-up time is too short, the conclusions that may be drawn lack credibility. Therefore, a reasonable plan should be proposed for the follow-up time of children after treatment with anti-VEGF.

The first strength of the article is that our meta-analysis adhered to the methodology recommendations of the Cochrane handbook. we conducted a thorough literature search. Second, the meta-analysis has a formal registered review protocol on PROSPERO, and our article was conducted and reported with rigorous methods following the PRISMA. Third, we included other parameters that may affect the refractive errors of ROP children, such as ACD, LT, AL, in our meta-analysis. Our article further strengthens the evidence of the safety of anti-VEGF drugs in children with ROP. However, our article also has certain limitations. Most of the literature we included are observational studies, and only 2 articles are RCTs, if more RCTs are included, we can draw more reliable conclusions.

Conclusions

In conclusion, the present meta-analysis showed that anti-VEGF therapy reduces myopia more effectively compared to laser treatment. Current evidence shows that anti-VEGF treatment has better refractive safety than laser therapy for children with ROP. Because intraocular injection of angiogenesis

factor inhibitors is increasingly applied, we need more high-quality RCTs to explore the issue further.

Footnotes

Contributors: Qi-Hang Kong and Xue-Song Mi conceived the idea of the article, Qi-Hang Kong and Xue-Song Mi did the literature search. Qi-Hang Kong, Xue-Song Mi, and Wai-kit Ming undertook the data acquisition and analysis. Qi-Hang Kong carried out the manuscript preparation. Xue-Song Mi and Wai-kit Ming were responsible for the revision of the manuscript. All authors have read and approved the final manuscript.

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Figure legends

Figure 1 Selection of studies for the meta-analysis

Figure 2 Forest plot of spherical equivalent.

Figure 3 Forest plot of the effect anti-VEGF therapy on spherical equivalent, according to the types of article included

Figure 4 Forest plot of axial length (AL)

Figure 5 Forest plot of anterior chamber depth (ACD).

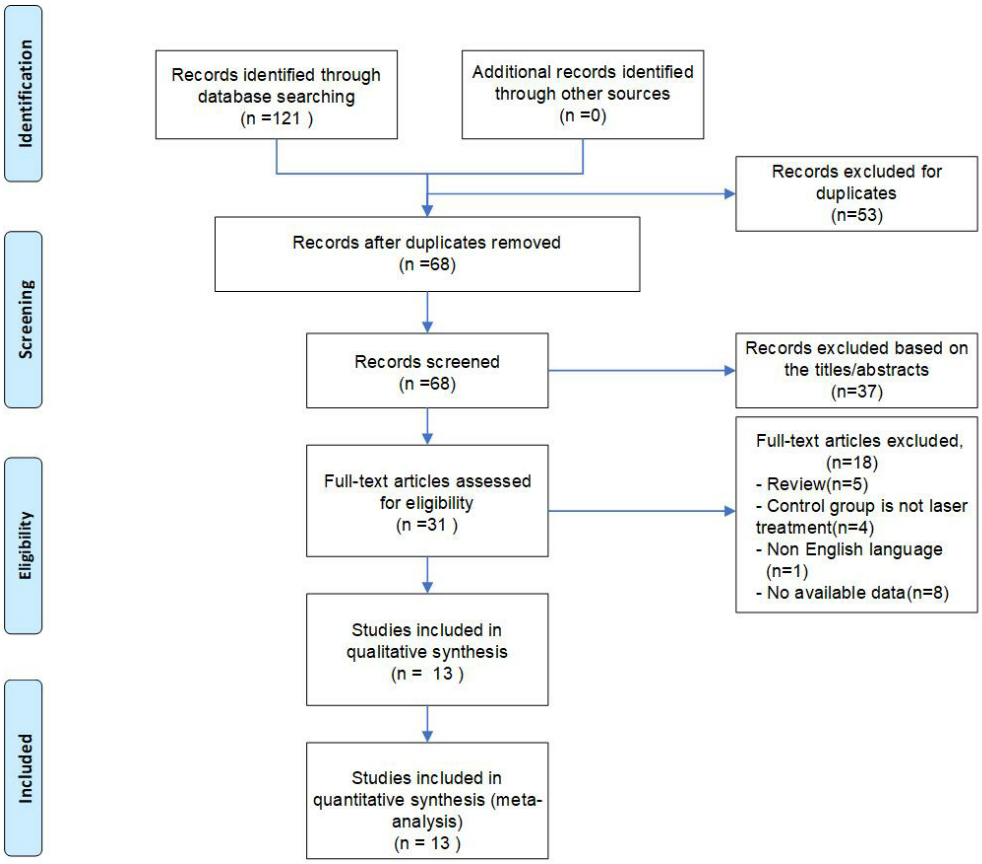

Figure1

215x184mm (120 x 120 DPI)

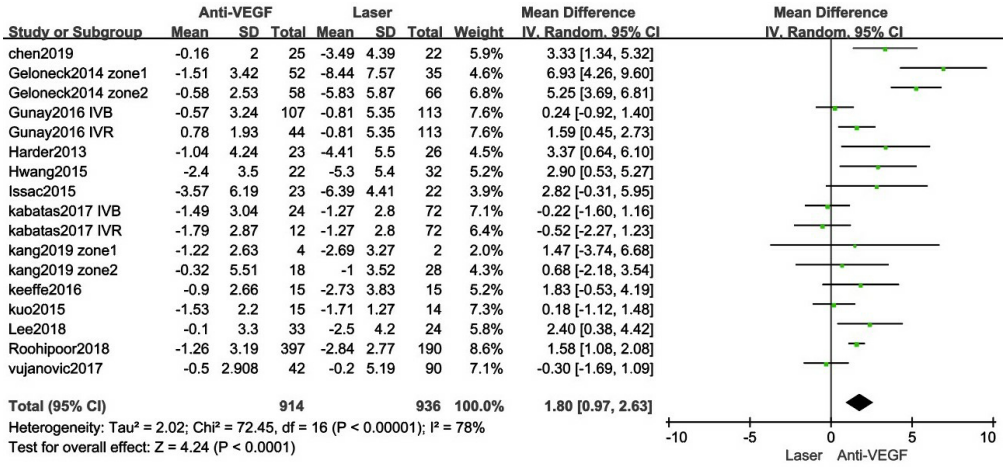

Figure2

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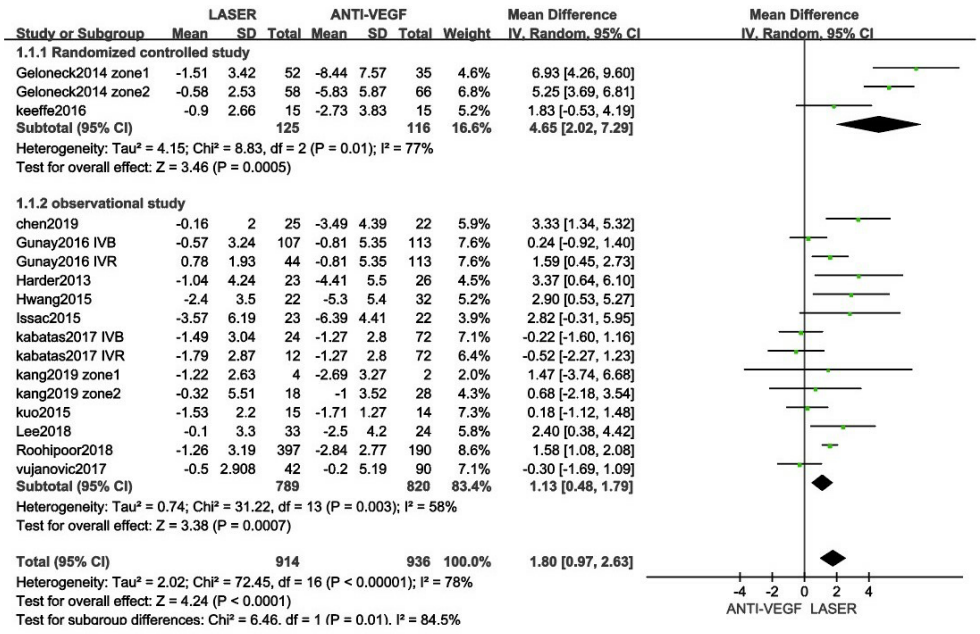

Figure3

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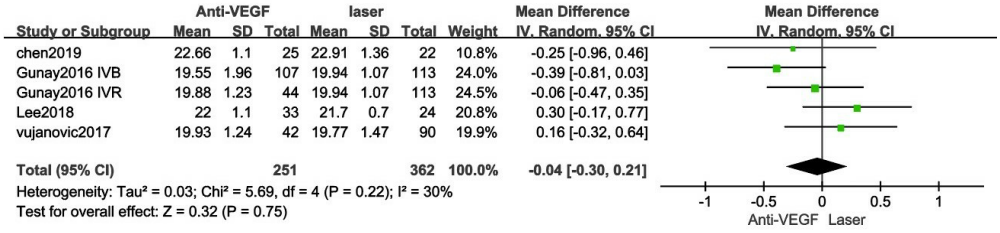

Figure4

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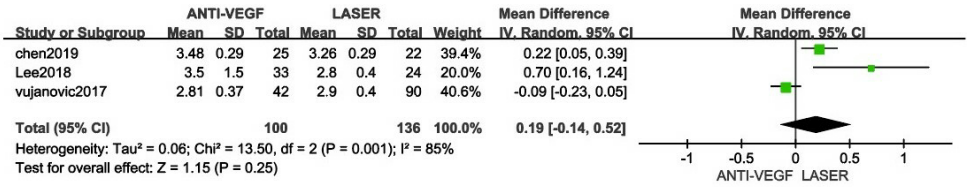


Figure5

298x67mm (96 x 96 DPI)

S1 strategy.

Detailed search strategy for PubMed

1. Retinopathy of Prematurity[MeSH]

2. Prematurity Retinopath*[Tiab] OR Retrolental Fibroplasia*[Tiab] OR Fibroplasia* Retrolental[Tiab]

3.1 OR 2

4. Anti-VEGF[MeSH]

5. Mvasi[Tiab] OR Avastin[Tiab] OR Ranibizumab[Tiab] OR aflibercept[Tiab] OR Anti-vascular endothelial growth factor[Tiab]

6.4 OR 5

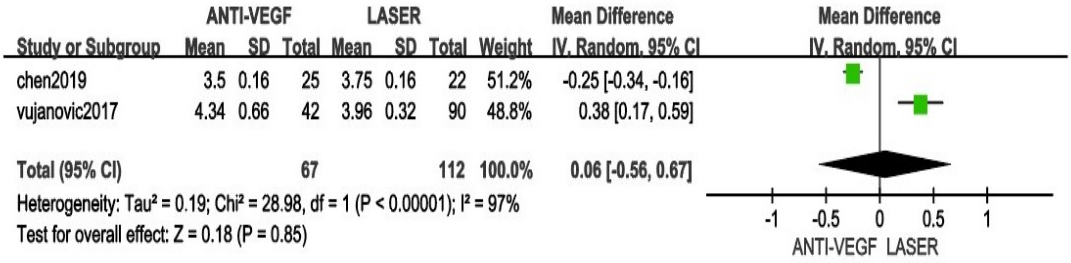
7. Error*,Refractive[MeSH]

8. Error*,Refractive[Tiab] OR Refractive Error*[Tiab] OR Disorder*,Refractive[Tiab] OR Ametropia[Tiab]

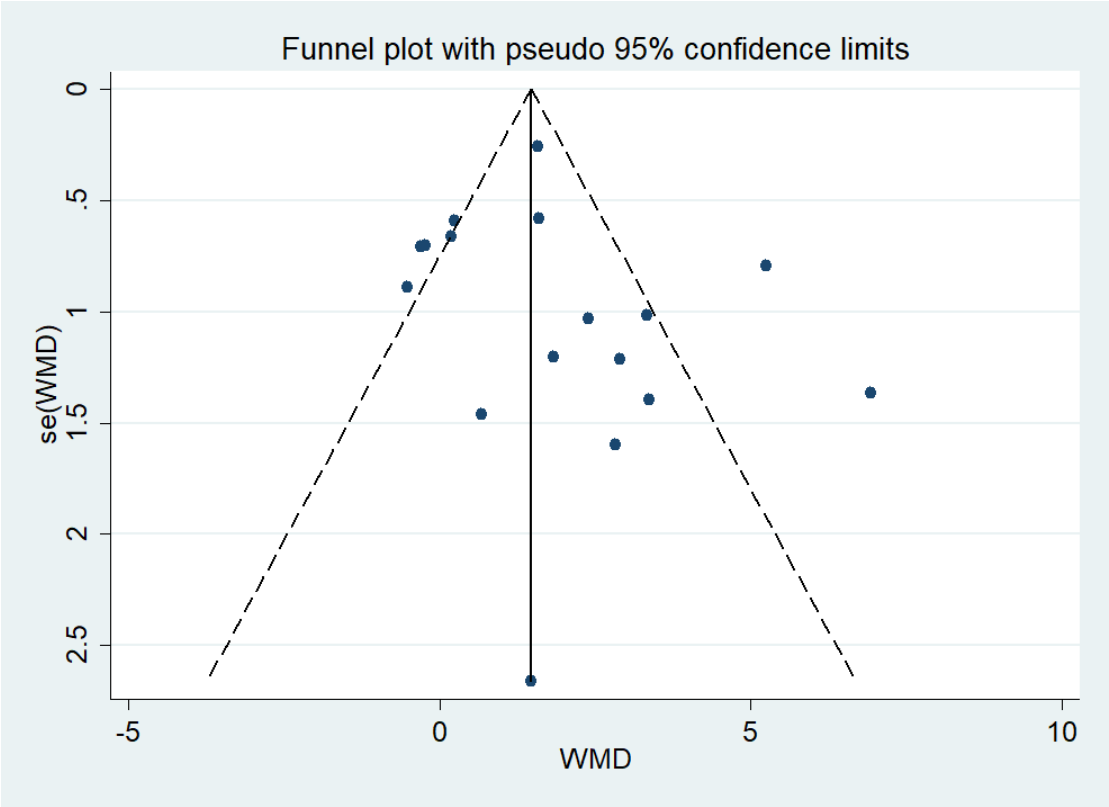
9.7 OR 8

10 3 AND 6 AND 9

S2 forest plot :Forest plot of lens thickness (LT).



S3 funnel plot: Publication bias was evaluated by the funnel plot.



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3,4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4,5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7,8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6,7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6(S1 strategy)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7,8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7,8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8,9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	13
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10(Table1)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13(S2 funnel plot)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18,19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Refractive Outcomes After Intravitreal Injection of Anti-vascular Endothelial Growth Factor Versus Laser Photocoagulation for Retinopathy of Prematurity: a Meta-analysis

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Key words: Retinopathy of Prematurity; Anti-VEGF; Refractive Errors; myopia

Abstract

Objective: To determine the effects of the intraocular injection of anti-vascular endothelial growth factor (anti-VEGF) drugs on the refractive status of infants with retinopathy of prematurity(ROP).

Design: Systematic review and meta-analysis of the refractive status of infants with ROP who receive anti-VEGF drugs .

Data sources:The PubMed,Web of Science,and EMBASE databases and the ClinicalTrials.gov website were searched up to June 2020.

Eligibility criteria when selecting studies: We included randomized controlled trials (RCTs) and observational studies that compared refractive errors between anti-VEGF drug and laser therapies.

Data extraction and synthesis: Data extraction and risk-of-bias assessments were conducted by two independent reviewers. We used a random-effects model to pool outcomes. The outcome measures were the spherical equivalents, axial length (AL), anterior chamber depth (ACD), and lens thickness (LT).

Results: Thirteen studies involving 1850 eyes were assessed: 914 in the anti-VEGF drug group, and 936 in the control (laser) group. Children who received anti-VEGF drug treatment had less myopia than those who received laser therapy (mean difference =1.80 diopter, 95% confidence interval =: 0.97 to 2.63, $P < 0.0001$, $I^2 = 78\%$). The AL, ACD, and LT did not reach statistical significance difference between the two groups.The current evidence indicates

that the refractive safety in children with ROP is better for anti-VEGF drug treatment than for laser therapy.

Conclusions:This meta-analysis indicates that anti-VEGF drug therapy results in less myopia compared with laser therapy. However, there are relatively few published articles on refractive errors in ROP , and so high-quality and powerful RCTs are needed in the future.

PROSPERO registration number: CRD42020160673

Strengths and limitations of this study

Our meta-analysis adhered to the methodology recommendations of the Cochrane Handbook. We conducted a thorough literature search.

The article describes a review protocol that is formally registered on PROSPERO, and the study was conducted and reported on using rigorous methods following the PRISMA statement.

We included other parameters that may affect the refractive errors in children with ROP in our meta-analysis, such as ACD, LT,and AL

The refractive error measures were from different follow-up time points across studies, this may confound the evaluation of refractive error differences between anti-VEGF and laser

Most of the included studies had an observational design,with only two RCTs being included, The inclusion of more RCTs would have allowed more-reliable conclusions to be drawn.

Introduction

Retinopathy of prematurity (ROP) is a common cause of blindness in developed countries and its prevalence is increasing in developing countries.[1] Characterized by retinal ischemia, aberrant angiogenesis, fibrovascular proliferation, and progressive vitreoretinal traction, ROP accounts for 14% and 20% of cases of childhood blindness in the United States and developing countries,respectively.[2]

ROP is a unique retinal vascular proliferative disease occurring in premature and low-birth-weight infants.[3] Retinal vascularization normally occurs at around 12 weeks of gestation and is completed by 36-40 weeks. This prolonged development period means that the retinal system is immature when infants leave the uterus prematurely. The loss of the maternal interaction environment and exposure to high oxygen levels in premature infants can lead to the cessation of retinal vascularization, damage to the capillary endothelium, hypoxia of the retinal blood vessels, and stimulation of fibrovascular tissue proliferation, and might even finally lead to traction retinal detachment.[4]

Laser photocoagulation has previously been the mainstay treatment for ROP. While this intervention is effectivie and safe, a few defects can remain, such as high myopia, visual field loss, and retinal destruction. An intensive study of ROP found that the levels of vascular endothelial growth factor (VEGF) were markedly elevated in the vitreous of eyes at stage-4 ROP.[5] In a normally developing retina, VEGF promotes the development of blood vessels from the optic nerve to the periphery, whereas the overexpression of VEGF in preterm

infants leads to abnormal vascular proliferation.[6] This situation has prompted, researchers to use anti-VEGF drugs to treat ROP. Many studies have shown that the intravitreal injection of anti-VEGF drugs may be an effective clinical intervention for ROP.[7, 8 9] However, the effects of this intervention are relatively short term, while its long-term complications remain unclear, such as postoperative refractive errors. Kang et al.[10] showed that anti-VEGF drugs do not cause refractive errors after ROP treatment, while Kabatas et al.[11] found that effects of the intravitreal injection of anti-VEGF drugs did not differ significantly from those of laser photocoagulation, with both potentially causing refractive errors.

The increasing clinical application of anti-VEGF drugs makes it important to know whether these drugs can also cause refractive errors in children with ROP. Hence, the purpose of the present meta-analysis was to determine the effects of anti-VEGF drugs on the refractive status of ROP compared with laser treatment, and to verify their clinical safety. The outcome measures considered in this study were the spherical equivalents (SE), axial length (AL), anterior chamber depth (ACD),and lens thickness (LT).

Methods

Our study is reported on here in accordance with the PRISMA guidelines for meta-analyses.[12] The study has been registered on PROSPERO (registration number CRD42020160673).

Data sources and search strategy.

From their inceptions to January 2020, we searched the PubMed, Web of Science, EMBASE databases, and the ClinicalTrials.gov website using keywords and medical subject headings. Only studies reported on in English were considered for inclusion. We also searched the reference lists of the selected articles to identify any other relevant articles. The search termsincluded “retinopathy of prematurity,” “prematurity retinopathy,” “retrolental fibroplasia,” “fibroplasia, retrolental,” “ROP,” “anti-VEGF,” “bevacizumab,” “Avastin,” “Lucentis,” “ranibizumab,” “aflibercept,” “anti-vascular endothelial growth factor,” “Mvasi,” and “refractive errors,” “disorders, refractive,” and “ametropias.” The search strategy is detailed in the S1 strategy(online supplementary material).

Study selection and eligibility criteria.

Each study was independently screened by two of the authors (Q.H.K.and M.X.S),with discrepancies between them resolved through discussion with the third author (W.M.). The following inclusion criteria were applied : (1) children who had been clearly diagnosed with ROP, (2) subjects in the intervention group had received an intraocular injection of an anti-VEGF drug that can be used in children with ROP,(3) subjects in the control group had received treatment of the eye using a retinal argon or diode laser., (4)the outcome of interest was the refractive status of the treated children with ROP , including

SE and ocular biometric structural features such as AL, ACD, and LT,and (5) the study design was a randomized controlled trial(RCT) or an observational study. We excluded children with stage-4 ROP,stage-5 ROP, or other eye diseases such as congenital cataract or glaucoma prior to treatment.

Data extraction and quality assessment.

The following information was extracted for the included studies: name of the first author, publication year, sample size, number of eyes, GA (gestational age), BW (birth weight), follow-up time, type of anti-VEGF drug, dose of anti-VEGF drug , and results data (SE, AL, ACD,and LT). When two anti-VEGF drugs had been applied in a study,, we extracted the data separately and compared the data with the control group.

We entered the extracted data into an Excel file. Two of the authors (Q.H.K and M.X.S.) assessed the quality of studies using the Newcastle-Ottawa Scales(NOS).[13] The NOS consists of four items for subject selection (maximum 4 points), one item for comparability between groups (maximum 2 points), and three items for outcome measurement (maximum 3 points). The maximum score is therefore 9 points, with studies considered to be of moderate quality having scores of 4–6, and those of high quality having scores of 7–9.[14]

Statistical analysis.

The weighted mean differences (WMDs) with 95% confidence intervals (Cis)

were calculated for continuous variables. Heterogeneity between the included studies was assessed using the I^2 statistic. I^2 values of 25%-50%, 50%-75%,75%-100% were considered to indicate low, moderate, and high heterogeneity,resppectively.[15] Due to the posstibility of heterogeneity being present between studies, we used a more-conservative version of the random-effects model.

A visual funnel plot was used to evaluate publication bias,with an asymmetric plot indicating that publication bias was present. Egger's test was further used to provide accurate assessments of publication bias, with if $P< 0.05$, considered to indicate some degree of publication bias.

All statistical analyses were performed using RevMan software (version 5.3, Nordic Cochrane Centre) and Stata software (version 12.0, Stata Corporation).

Results

Literature search.

The initial literature search identified 121 records. After screening the titles and Abstracts, 31 potentially eligible studies were assessed for inclusion. After reading the full texts ,13 studies were finally included in the present meta-analysis. The study selection process is illustrated in **Figure 1**.

The 13 selected studies comprised 2 RCTs[16, 17] and 11 observational studies[11, 18-27]. According to the scoring criteria of the NOS, 11 studies were evaluated as being of high quality, while 2 were evaluated as being of moderate quality. The NOS score of the included studies ranged from 6 to 8,with a median of 8. All of

the articles had been published between 2013 and 2019. The sample sizes in the studies ranged from 12 to 397, with a total of 1850 eyes: 914 in the anti-VEGF drug group and 936 in the control group. The included anti-VEGF drugs were bevacizumab and ranibizumab.,with 1.of these drugs administered in 12 studies and 2 drugs administered in 1 study.The dose of anti-VEGF drugs also varied among the included studies,from a minimum of 0.2mg to a maximum of was 1.25mg, with most of the studies using 0.625 mg.

After injecting anti-VEGF drugs, children with ROP were followed regularly for more than 6 months, ranging from 9 months to 5 years. SE values were reported for all of the 13 included studies, while ALs, ACDs, and LTs were reported for 4, 3, and 2 studies, respectively. We presented the main information within the included studies in our meta-analysis (**Table 1**)

Table 1: Main Characteristics of Studies Included in the Meta-analysis

First author/year	region	Group	patients /eyes(n)	GA(weeks) (mean±SD)	BW(g) (mean±SD)	Follow-up (months)	Type of Anti-VEGF	Anti-VEGF dose(mg)	NOS score
Harder 2013[18]	Germany	Anti-VEGF laser	12/23 13/26	25.20 ± 1.60 25.30± 1.80	622.00 ± 153.00 717.00 ± 197.00	12	bevacizumab	0.375 or 0.625	7
Hwang 2015[19]	American	Anti-VEGF laser	11/22 17/32	NA	668.10 ± 127.30 701.40 ± 118.80	21.7 32.5	bevacizumab	0.625	8
Kabataş 2017[11] ⋆	Turkey	Anti-VEGF laser	12/24 36/72	26.10 ± 2.27 27.70 ± 2.70	841.00 ± 235.00 1,112.00 ± 362.00	18	bevacizumab	0.625	8
Kabataş 2017[11] ⋆	Turkey	Anti-VEGF laser	6/12 36/72	26.00 ± 1.26 27.70 ± 2.70	840.00 ± 177.00 1,112.00 ± 362.00	18	ranibizumab	0.25	8
Kuo 2015[20]	Taiwan	Anti-VEGF laser	15/15 14/14	27.33 ± 2.94 27.43± 2.93	1,079.67 ± 357.48 1,006.79 ± 327.65	3 years of age	bevacizumab	0.5	7
Kang 2019[21]	Korea	Anti-VEGF laser	12/22 15/30	27.40 ± 2.00 34.00 ± 2.90	983.20 ± 265.60 961.00 ± 286.50	4 years of age	bevacizumab ranibizumab	0.625 0.2	7
Isaac 2015[22]	Canada	Anti-VEGF laser	13/23 12/22	25.20 ± 1.40 25.00 ± 1.10	722.00 ± 131.00 674.00 ± 175.00	16.00±6.00 6.00±3.00	bevacizumab	0.625	8
Vujanović2017[23]	Serbia	Anti-VEGF laser	21/42 45/90	29.00 ± 4.00 30.00 ± 4.00	1,175.00 ± 425.00 1,200.00 ± 500.00	9	bevacizumab	0.625	8

Table 1 *(continued)*

First author/year	region	Group	patients /eyes(n)	GA(weeks) (mean±SD)	BW(g) (mean±SD)	Follow-up (months)	Type of Anti-VEGF	Anti-VEGF dose(mg)	NOS score
Gunay 2016[24] ⋆	Turkey	Anti-VEGF laser	55/107 57/113	27.31 ± 2.18 28.23 ± 2.50	1005.29 ±411.19 1119.47 ± 336.96	19.40±6.43 20.68±6.89	bevacizumab	0.625	8
Gunay 2016[24] ⋆	Turkey	Anti-VEGF laser	22/44 57/113	27.95 ± 2.90 28.23 ± 2.50	1195.90 ± 466.98 1119.47 ± 336.96	18.96±4.79 20.68±6.89	ranibizumab	0.25	8
Chen 2019[25]	Taiwan	Anti-VEGF laser	13/25 12/22	26.46 ±1.51 25.50 ±1.24	862.54 ±197.65 815.83 ±151.07	NA	bevacizumab	0.625	7
Lee 2018[26]	Taiwan	Anti-VEGF laser	17/33 13/24	26.60 ± 1.60 26.60 ± 2.50	874.10 ± 228.70 803.10 ± 144.90	> 48	bevacizumab	0.625	6
Roohipoor2018[27]	Iran	Anti-VEGF laser	NA/397 NA/190	27.8	1146	> 12	bevacizumab	0.625	8
Geloneck2014[16]*	American	Anti-VEGF laser	56/110 53/101	24.3	625	2.5 years of age	bevacizumab	0.625	8
O'Keeffe2016[17] *	Irish	Anti-VEGF laser	15/15 15/15	25±1.25	780±135	60	bevacizumab	1.25	6

***:** RCT, Randomized Controlled Trial; NOS: Newcastle-Ottawa Scale; NA: not applicable; GA: gestational age; BW: birth weight;

⋆ : There are two types of Anti-VEGF drugs included in the literature, so the details are listed separately

Main outcomes

Spherical equivalent. The SE values were reported for 914 eyes in the anti-VEGF drug group and 936 eyes in the control group. (**Figure 2**). The SE values were higher in the anti-VEGF drug group than in the control group (MD=1.80 diopter, 95% CI=0.97 to 2.63),with a high heterogeneity (I^2 = 78%). The findings of the subgroup analysis of the SE according to type of article are summarized in **Figure 3.** At the same time, according to different types of anti-VEGF drugs(Online supplementary material S2 forest plot) and different follow-up time (Online supplementary material S3 forest plot), we conducted a subgroup analysis.

Axial length. Three articles [23, 25, 26] reported the AL, with 251 eyes in the anti-VEGF drug group and 362 eyes in the control group. (**Figure 4**). There was no signtificant difference in the AL between the groups (MD=-0.04mm, 95%=CI: -0.30 to 0.21), and the heterogeneity was low (I^2 = 30%).

Anterior chamber depth. Three articles[23, 25, 26] reported the ACD in children with ROP who were or were not taking anti-VEGF drugs. We found no difference in the ACD between the anti-VEGF drug and control groups(MD=0.19mm; 95% CI=-0.14 to 0.52, I^2 = 85%).(**Figure 5**) There was high heterogeneity(I^2 = 85%), but excluding Vujanović's study in the sensitivity analysis resulted in moderate heterogeneity (MD= 0.39mm; 95% CI=-0.06 to 0.84, I^2 = 64%).

Lens thickness. Two articles[23, 25] reported the LT,which did not differ

significantly between the anti-VEGF drug and laser groups (MD=0.06mm; 95% CI: -0.56 to 0.67, P =0.85), and I^2 was 97%. (online supplementary material: S4 forest plot).

Publication bias

Visual examinations of funnel plots constructed using Stata software. and also statistical calculations using in Egger's test did not reveal any publication bias (P =0.401). (online supplementary material S5 funnel plot)

Discussion

The present meta-analysis identified that 13 previous studies have investigated the association between treatments and refractive errors among children with ROP, and analyzed SE, AL, ACD, and LT. A significant difference in SE was found between the two study groups.,This means that anti-VEGF drug treatment reduces myopia in children with ROP compared with laser treatment, as consistently found in both the comprehensive and subgroup analyses. However, no significant difference were found in the other variables analyzed in this study.

Meta-analyses of similar subjects have also been reported.[28] The meta-analysis of Tan et al. included 7 articles covering 519 eyes, but this was limited to the anti-VEGF drug bevacizumab. Although the main finding of our meta-analysis was consistent with previous meta-analyses, there are some differences between them. Firstly, our study analyzed the largest amount of data(13 articles covering 1850 eyes) and included some recently published

literature, which increased the statistical power of the analyses. Secondly, in addition to the anti-VEGF drug bevacizumab, another anti-VEGF drug that is commonly used in clinical practice was also included (ranibizumab).,which makes the present conclusions closer to clinical reality. Thirdly,we added other ocular parameters to investigate how anti-VEGF drug and laser therapies affect refractive errors:ACD, LT, and AL. A previous study showed that these ocular refractive parameters may be related to myopic adults with ROP,[29] but no evidence was provided for laser treatment and anti-VEGF drug treatment exerting different effects on the refractive status in children with ROP.We therefore analyzed these ocular parameters in laser and anti-VEGF drug groups, with the obtained results providing further evidence that anti-VEGF drug treatment is safe for children with ROP.

This meta-analysis of 13 articles synthesized the literature to evaluate the refractive safety of anti-VEGF drugs for children with ROP,and has shown that anti-VEGF drug treatment provides better refractive results than does laser treatment. As seen in previous studies, myopia was reduced more by anti-VEGF drug therapy than by laser treatment in the current study. Most previous studies have quantified refractive errors using SE values,since this parameter is considered the primary measure of such errors,and so we also used this parameter to explore group differences .

Kuo et al[20] and Issec et al.[22] reported that refractive errors did not differ significantly between anti-VEGF drug and laser groups. However, our meta-

analysis found that anti-VEGF drug therapy reduces myopia and refractive errors more that does laser treatment. Two factors may explain this difference.(1)both of the previous studies included small samples ,and(2) a higher proportion of the children included in the present study had severe ROP. The present findings indicate that anti-VEGF drug therapy may be an alternative to laser therapy for reducing refractive errors in children with ROP. Our subgroup analysis found that anti-VEGF drug therapy exerted better effects on refractive errors than did laser therapy, based on findings in both RCTs and observational studies.

Laser therapy has been considered the first choice of treatment for ROP and has well-established safety and efficacy.However, this approach results in the retina being permanently cauterized, leading to inadequate vascularization and the risk of visual field loss, high myopia, and cataracts. Regarding refraction, it has also been reported that laser treatment may be a risk factor for refractive errors in children with ROP.[30] Therefore, the impact of future damage to the refractive status that may result from laser treatment needs to be considered when treating children with ROP, indicating the need to find a treatment method with increased effectiveness and safety. A previous in-depth study of the ROP mechanism found that the intraocular injection of an anti-VEGF drug may be a good alternative to laser treatment.[22] The intraocular injection of anti-VEGF drugs has the advantages of less trauma and pain, and involving an easy procedure,which has resulted in it being increasingly used by a large number

of clinicians. This situation makes it essential to clarify the safety regarding refractive errors as soon as possible, and the present meta-analysis has provided good evidence for the refractive safety of anti-VEGF drugs.

Changes in the biometric structure of the eye—such as in ACD, LT, AL ,corneal curvature, and corneal diameter—may be related to increased refractive errors.[31-33] We therefore regard it as essential to consider the above indicators of ocular biometric structure when verifying the refractive status of children with ROP. Although there have been previous meta-analyses of refractive outcomes after treatment of ROP with anti-VEGF drug therapy, none of these meta-analyses explored the relationship between refractive outcomes and the biometric structure of the eye when comparing anti-VEGF drug and laser therapies.Our study found no significant intergroup differences in these parameters. There is also considerable debate about whether anti-VEGF drug treatment of ROP will induce changes in ocular parameters. Lee et al found that AL did not differ among different treatment groups. Gunay et al[34] reported that in children who receive anti-VEGF drug therapy, the AL might be related to the development of myopia and is not related to the ACD or LT. The BEAT-ROP believes that anti-VEGF drug treatment may facilitate the continuation of the local growth factor expression and signaling pathways, allowing the anterior segment to develop normally[16]. The small number of articles that have reported on the ocular biometric structure makes it difficult to draw definitive conclusions, and so more high-quality RCTs are needed to verify the impact of anti-VEGF

drugs on the ocular biometric structure.

We consider that future research should focus on two main aspects. Firstly, there is no unified standard for the optimal dose of anti-VEGF drugs to use in the treatment of ROP. Most clinical applications used doses are half of the adults, but if other doses of anti-VEGF treatment of ROP affect the result, we do not know, so in the future, a clear plan for the dose of anti-VEGF needs to be proposed. Secondly, there is no clear standard for the follow-up time of children with ROP. The conclusions that may be drawn lack credibility if the follow-up time is too short, and so the most-appropriate follow-up time of children after treatment with anti-VEGF drugs also needs to be determined.

The first strength of our meta-analysis is that it adhered to the methodology recommendations of the Cochrane Handbook, and included conducting a thorough literature search. Secondly, this meta-analysis has a formal registered review protocol on PROSPERO, and our investigations were conducted and reported with rigorous methods following the PRISMA statement. Thirdly, our meta-analysis included other parameters that may affect the refractive errors in children with ROP, such as ACD, LT, and AL. The results further strengthen the evidence for the safety of anti-VEGF drugs in children with ROP. However, our study also had certain limitations.First, the refractive error measures were from different follow-up time points across studies, this may confound the evaluation of refractive error differences between anti-VEGF and laser.Second,most of the included studies had an observational design,with

only two RCTs being included, The inclusion of more RCTs would have allowed more-reliable conclusions to be drawn.

Conclusions

In conclusion, the present meta-analysis has shown that anti-VEGF drug therapy reduces myopia more effectively than does laser treatment. The current evidence indicates that anti-VEGF drug treatment has better refractive safety than laser therapy for children with ROP. Since intraocular injections of angiogenesis factor inhibitors are increasingly being applied, more high-quality RCTs are required.

Footnotes

Contributors: Qi-Hang Kong and Xue-Song Mi conceived the idea of the article, Qi-Hang Kong and Xue-Song Mi did the literature search. Qi-Hang Kong, Xue-Song Mi, and Wai-kit Ming undertook the data acquisition and analysis. Qi-Hang Kong carried out the manuscript preparation. Xue-Song Mi and Wai-kit Ming were responsible for the revision of the manuscript. All authors have read and approved the final manuscript.

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Provenance and peer review: Not commissioned; externally peer-reviewed.

Data sharing statement: All data analyzed in this study are included in the article and its supplementary files.

Patient and Public Involvement: No patient involved

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Figure legends

Figure 1 Selection of studies for the meta-analysis

Figure 2 Forest plot of spherical equivalent.

Figure 3 Forest plot of the effect anti-VEGF therapy on spherical equivalent, according to the types of article included

Figure 4 Forest plot of axial length (AL)

Figure 5 Forest plot of anterior chamber depth (ACD).

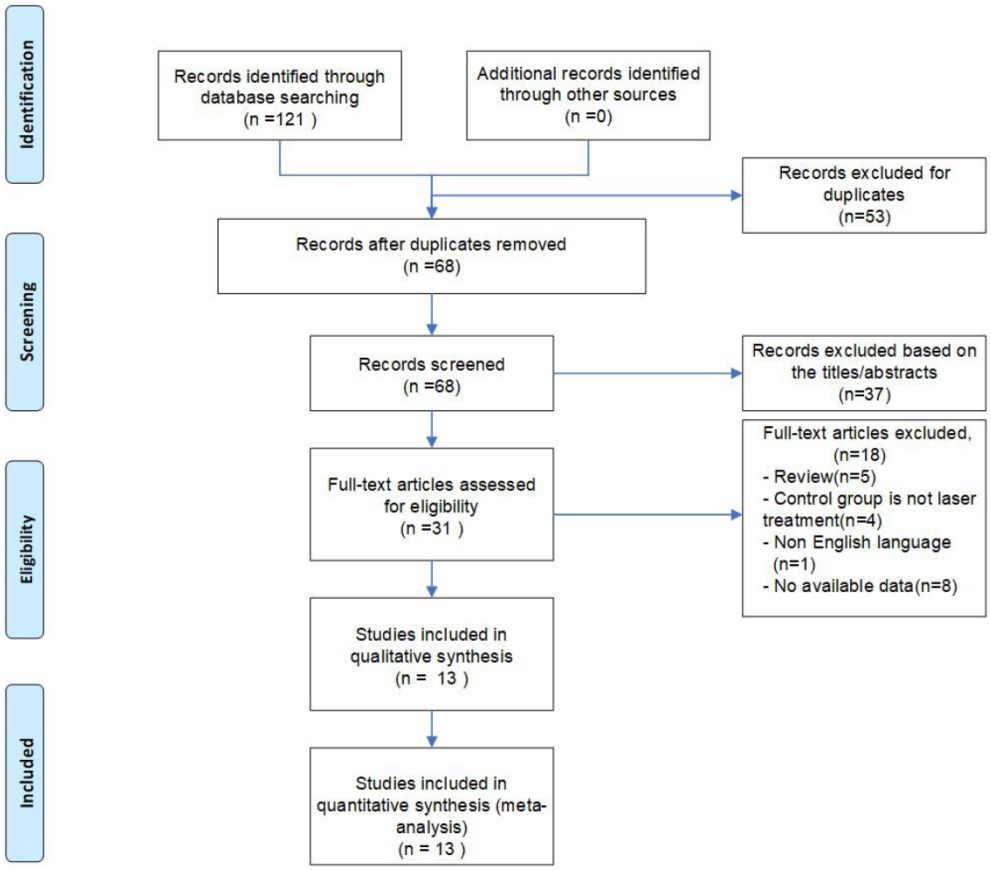

Identification
Screening
Eligibility
Included
Records identified through database searching (n =121)
Additional records identified through other sources (n =0)
Records excluded for duplicates (n=53)
Records after duplicates removed (n =68)
Records screened (n =68)
Records excluded based on the titles/abstracts (n=37)
Full-text articles assessed for eligibility (n =31)
Full-text articles excluded, (n=18)
- Review(n=5)
- Control group is not laser treatment(n=4)
- Non English language (n=1)
- No available data(n=8)
Studies included in qualitative synthesis (n = 13)
Studies included in quantitative synthesis (meta-analysis) (n = 13)

Figure 1

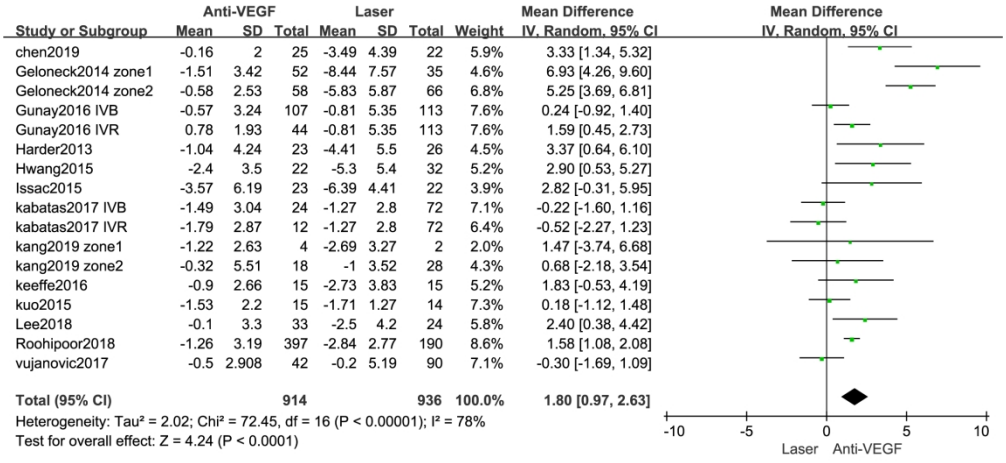

Anti-VEGF
Laser
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
chen2019 -0.16 2 25 -3.49 4.39 22 5.9% 3.33 [1.34, 5.32]
Geloneck2014 zone1 -1.51 3.42 52 -8.44 7.57 35 4.6% 6.93 [4.26, 9.60]
Geloneck2014 zone2 -0.58 2.53 58 -5.83 5.87 66 6.8% 5.25 [3.69, 6.81]
Gunay2016 IVB -0.57 3.24 107 -0.81 5.35 113 7.6% 0.24 [-0.92, 1.40]
Gunay2016 IVR 0.78 1.93 44 -0.81 5.35 113 7.6% 1.59 [0.45, 2.73]
Harder2013 -1.04 4.24 23 -4.41 5.5 26 4.5% 3.37 [0.64, 6.10]
Hwang2015 -2.4 3.5 22 -5.3 5.4 32 5.2% 2.90 [0.53, 5.27]
Issac2015 -3.57 6.19 23 -6.39 4.41 22 3.9% 2.82 [-0.31, 5.95]
kabatas2017 IVB -1.49 3.04 24 -1.27 2.8 72 7.1% -0.22 [-1.60, 1.16]
kabatas2017 IVR -1.79 2.87 12 -1.27 2.8 72 6.4% -0.52 [-2.27, 1.23]
kang2019 zone1 -1.22 2.63 4 -2.69 3.27 2 2.0% 1.47 [-3.74, 6.68]
kang2019 zone2 -0.32 5.51 18 -1 3.52 28 4.3% 0.68 [-2.18, 3.54]
keeffe2016 -0.9 2.66 15 -2.73 3.83 15 5.2% 1.83 [-0.53, 4.19]
kuo2015 -1.53 2.2 15 -1.71 1.27 14 7.3% 0.18 [-1.12, 1.48]
Lee2018 -0.1 3.3 33 -2.5 4.2 24 5.8% 2.40 [0.38, 4.42]
Roohipoor2018 -1.26 3.19 397 -2.84 2.77 190 8.6% 1.58 [1.08, 2.08]
vujanovic2017 -0.5 2.908 42 -0.2 5.19 90 7.1% -0.30 [-1.69, 1.09]
Total (95% CI) 914 936 100.0% 1.80 [0.97, 2.63]
Heterogeneity: Tau² = 2.02; Chi² = 72.45, df = 16 (P < 0.00001); I² = 78%
Test for overall effect: Z = 4.24 (P < 0.0001)
-10
-5
0
5
10
Laser
Anti-VEGF

Figure 2

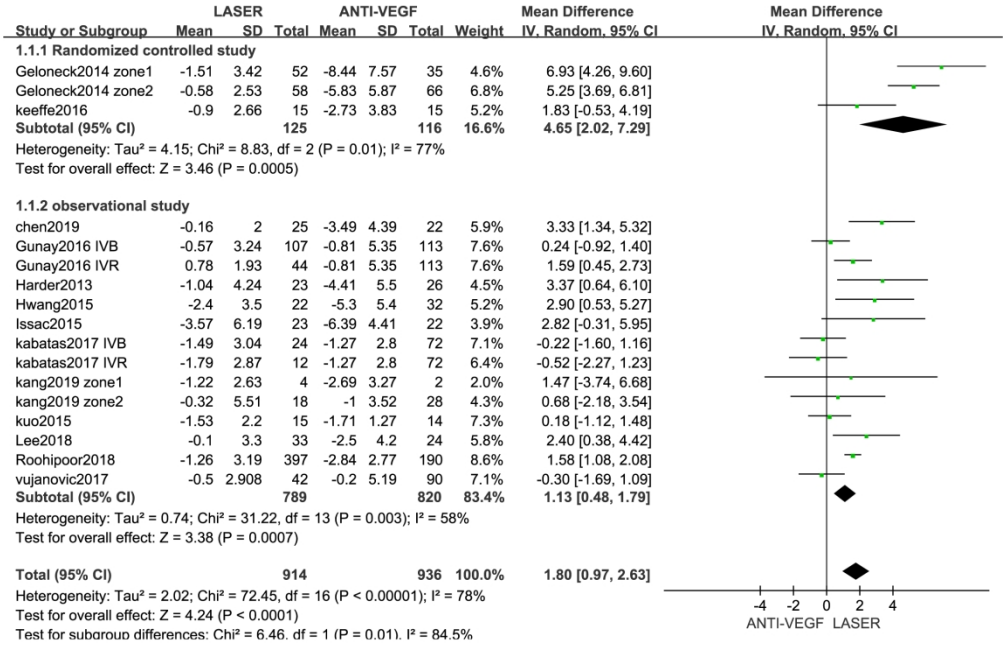

LASER
ANTI-VEGF
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
1.1.1 Randomized controlled study
Geloneck2014 zone1 -1.51 3.42 52 -8.44 7.57 35 4.6% 6.93 [4.26, 9.60]
Geloneck2014 zone2 -0.58 2.53 58 -5.83 5.87 66 6.8% 5.25 [3.69, 6.81]
keeffe2016 -0.9 2.66 15 -2.73 3.83 15 5.2% 1.83 [-0.53, 4.19]
Subtotal (95% CI) 125 116 16.6% 4.65 [2.02, 7.29]
Heterogeneity: Tau² = 4.15; Chi² = 8.83, df = 2 (P = 0.01); I² = 77%
Test for overall effect: Z = 3.46 (P = 0.0005)
1.1.2 observational study
chen2019 -0.16 2 25 -3.49 4.39 22 5.9% 3.33 [1.34, 5.32]
Gunay2016 IVB -0.57 3.24 107 -0.81 5.35 113 7.6% 0.24 [-0.92, 1.40]
Gunay2016 IVR 0.78 1.93 44 -0.81 5.35 113 7.6% 1.59 [0.45, 2.73]
Harder2013 -1.04 4.24 23 -4.41 5.5 26 4.5% 3.37 [0.64, 6.10]
Hwang2015 -2.4 3.5 22 -5.3 5.4 32 5.2% 2.90 [0.53, 5.27]
Issac2015 -3.57 6.19 23 -6.39 4.41 22 3.9% 2.82 [-0.31, 5.95]
kabatas2017 IVB -1.49 3.04 24 -1.27 2.8 72 7.1% -0.22 [-1.60, 1.16]
kabatas2017 IVR -1.79 2.87 12 -1.27 2.8 72 6.4% -0.52 [-2.27, 1.23]
kang2019 zone1 -1.22 2.63 4 -2.69 3.27 2 2.0% 1.47 [-3.74, 6.68]
kang2019 zone2 -0.32 5.51 18 -1 3.52 28 4.3% 0.68 [-2.18, 3.54]
kuo2015 -1.53 2.2 15 -1.71 1.27 14 7.3% 0.18 [-1.12, 1.48]
Lee2018 -0.1 3.3 33 -2.5 4.2 24 5.8% 2.40 [0.38, 4.42]
Roohipoor2018 -1.26 3.19 397 -2.84 2.77 190 8.6% 1.58 [1.08, 2.08]
vujanovic2017 -0.5 2.908 42 -0.2 5.19 90 7.1% -0.30 [-1.69, 1.09]
Subtotal (95% CI) 789 820 83.4% 1.13 [0.48, 1.79]
Heterogeneity: Tau² = 0.74; Chi² = 31.22, df = 13 (P = 0.003); I² = 58%
Test for overall effect: Z = 3.38 (P = 0.0007)
Total (95% CI) 914 936 100.0% 1.80 [0.97, 2.63]
Heterogeneity: Tau² = 2.02; Chi² = 72.45, df = 16 (P < 0.00001); I² = 78%
Test for overall effect: Z = 4.24 (P < 0.0001)
Test for subgroup differences: Chi² = 6.46, df = 1 (P = 0.01), I² = 84.5%
-4 -2 0 2 4
ANTI-VEGF LASER

Figure 3

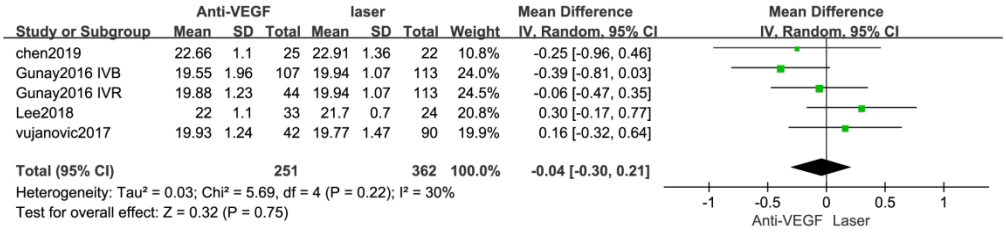

Anti-VEGF
laser
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
chen2019 22.66 1.1 25 22.91 1.36 22 10.8% -0.25 [-0.96, 0.46]
Gunay2016 IVB 19.55 1.96 107 19.94 1.07 113 24.0% -0.39 [-0.81, 0.03]
Gunay2016 IVR 19.88 1.23 44 19.94 1.07 113 24.5% -0.06 [-0.47, 0.35]
Lee2018 22 1.1 33 21.7 0.7 24 20.8% 0.30 [-0.17, 0.77]
vujanovic2017 19.93 1.24 42 19.77 1.47 90 19.9% 0.16 [-0.32, 0.64]
Total (95% CI) 251 362 100.0% -0.04 [-0.30, 0.21]
Heterogeneity: Tau² = 0.03; Chi² = 5.69, df = 4 (P = 0.22); I² = 30%
Test for overall effect: Z = 0.32 (P = 0.75)
-1
-0.5
0
0.5
1
Anti-VEGF
Laser

Figure 4

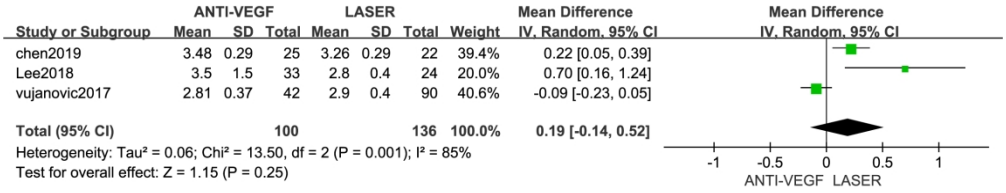

ANTI-VEGF
LASER
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
chen2019 3.48 0.29 25 3.26 0.29 22 39.4% 0.22 [0.05, 0.39]
Lee2018 3.5 1.5 33 2.8 0.4 24 20.0% 0.70 [0.16, 1.24]
vujanovic2017 2.81 0.37 42 2.9 0.4 90 40.6% -0.09 [-0.23, 0.05]
Total (95% CI) 100 136 100.0% 0.19 [-0.14, 0.52]
Heterogeneity: Tau² = 0.06; Chi² = 13.50, df = 2 (P = 0.001); I² = 85%
Test for overall effect: Z = 1.15 (P = 0.25)
-1
-0.5
0
0.5
1
ANTI-VEGF
LASER

Figure 5

S1 strategy.

Detailed search strategy for PubMed

1. Retinopathy of Prematurity[MeSH]

2. Prematurity Retinopath*[Tiab] OR Retrolental Fibroplasia*[Tiab] OR Fibroplasia* Retrolental[Tiab]

3.1 OR 2

4. Anti-VEGF[MeSH]

5. Mvasi[Tiab] OR Avastin[Tiab] OR Ranibizumab[Tiab] OR aflibercept[Tiab] OR Anti-vascular endothelial growth factor[Tiab]

6.4 OR 5

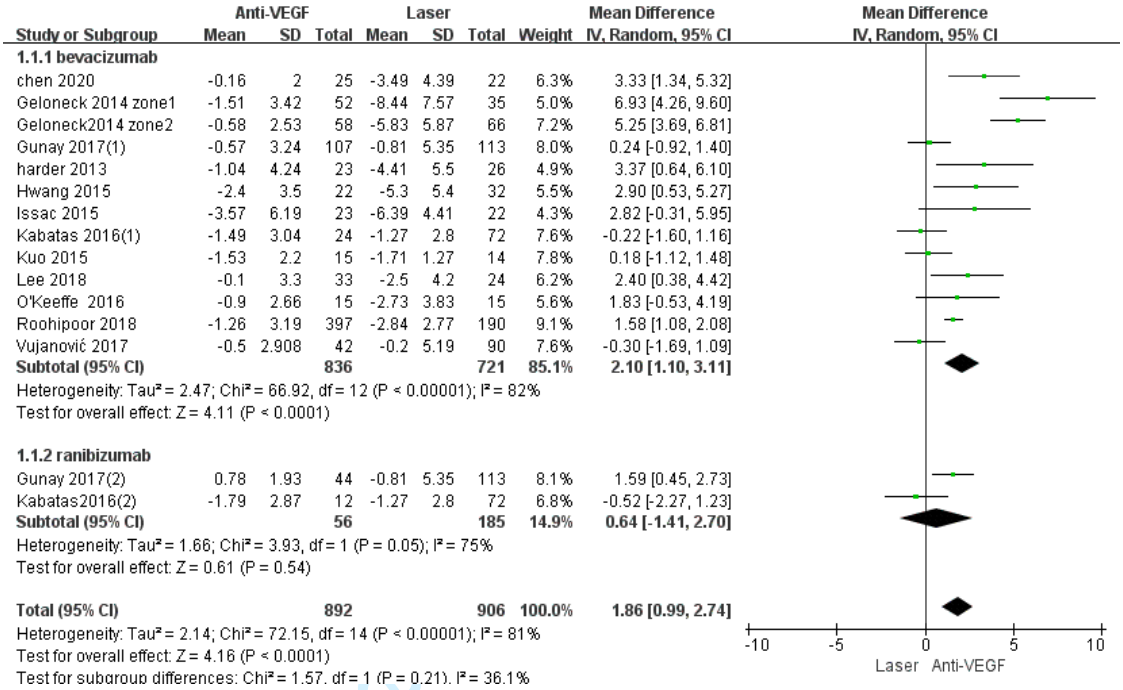
7. Error*,Refractive[MeSH]

8. Error*,Refractive[Tiab] OR Refractive Error*[Tiab] OR Disorder*,Refractive[Tiab] OR Ametropia[Tiab]

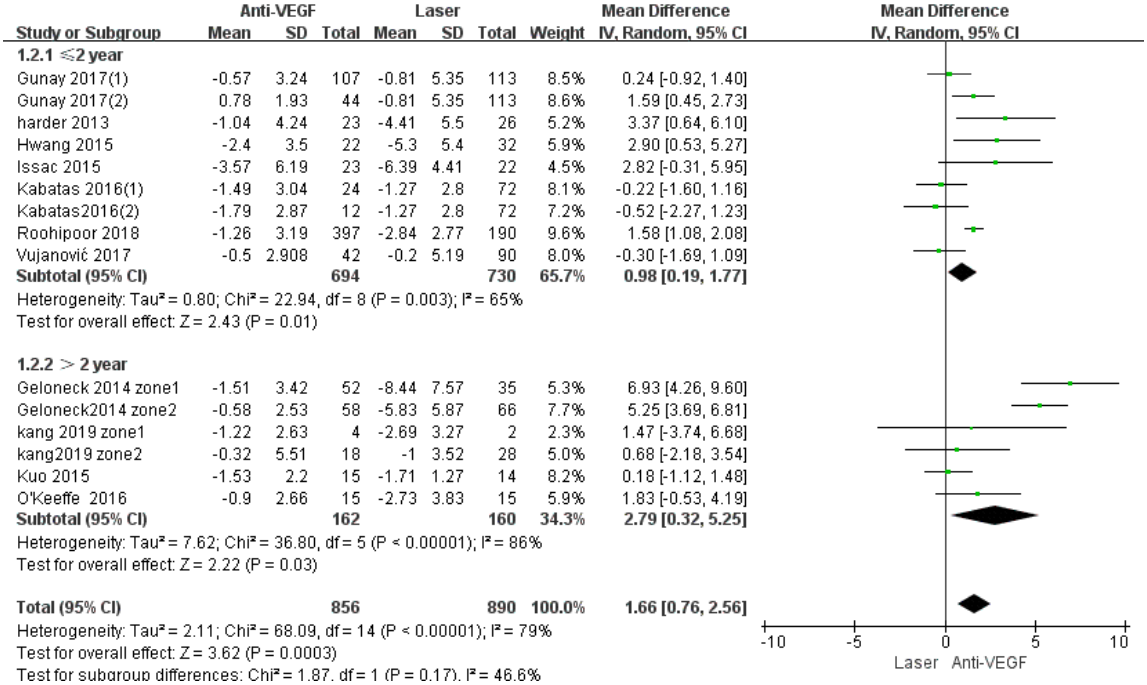
9.7 OR 8

10 3 AND 6 AND 9

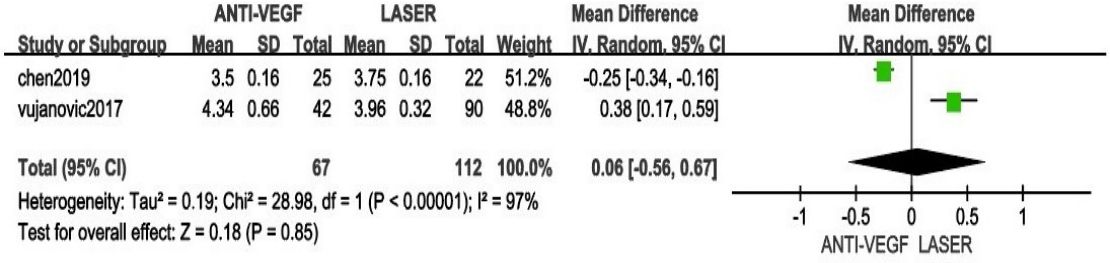
S2 forest plot : Forest plot of the effect of different anti-VEGF drugs on spherical equivalent.



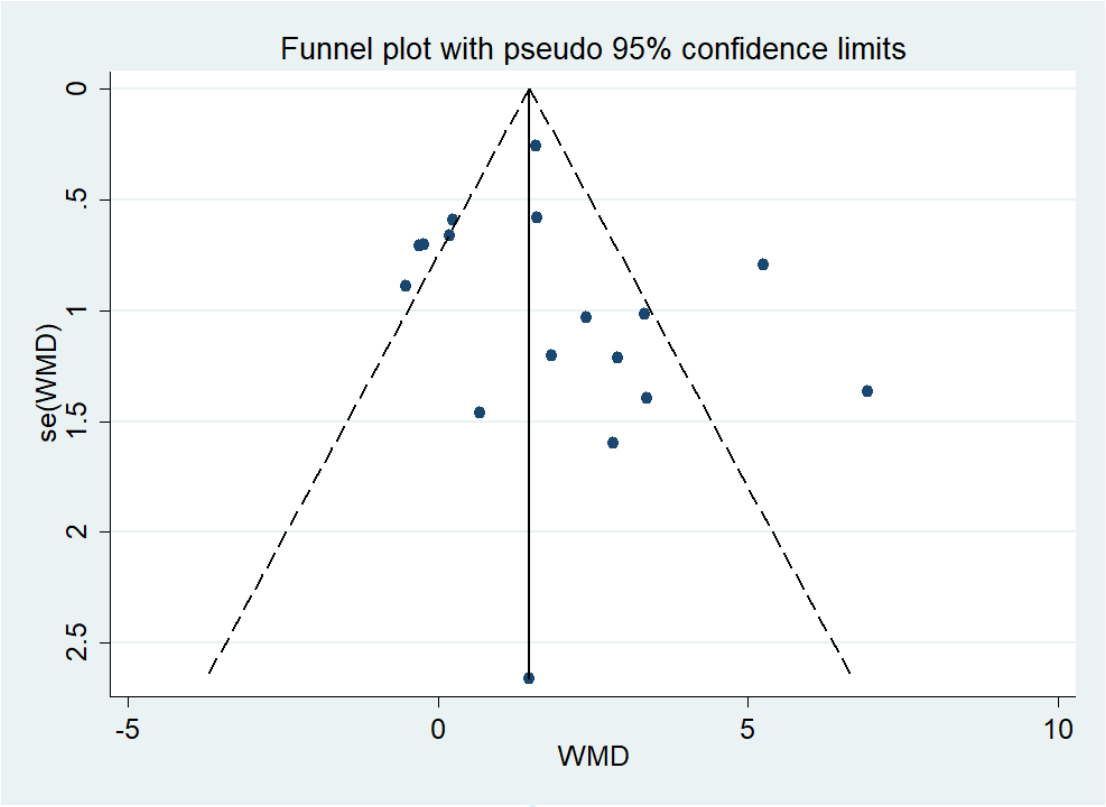
S3 forest plot : Forest plot of the influence of different follow-up time on spherical equivalent.



S4 forest plot :Forest plot of lens thickness (LT).



S5 funnel plot: Publication bias was evaluated by the funnel plot.



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3,4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4,5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7,8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6,7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6(S1 strategy)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7,8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7,8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8,9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	13
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10(Table1)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13(S2 funnel plot)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18,19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Refractive Outcomes After Intravitreal Injection of Anti-vascular Endothelial Growth Factor Versus Laser Photocoagulation for Retinopathy of Prematurity: a Meta-analysis

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Refractive Outcomes After Intravitreal Injection of Anti-vascular Endothelial Growth Factor Versus Laser Photocoagulation for Retinopathy of Prematurity: a Meta-analysis

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Key words: Retinopathy of Prematurity; Anti-VEGF; Refractive Errors; myopia

Abstract

Objective: To determine the effects of the intraocular injection of anti-vascular endothelial growth factor (anti-VEGF) drugs on the refractive status of infants with retinopathy of prematurity(ROP).

Design: Systematic review and meta-analysis of the refractive status of infants with ROP who receive anti-VEGF drugs.

Data sources: The PubMed, Web of Science, and EMBASE databases and the ClinicalTrials.gov website were searched up to June 2020.

Eligibility criteria when selecting studies: We included randomized controlled trials (RCTs) and observational studies that compared refractive errors between anti-VEGF drug and laser therapies.

Data extraction and synthesis: Data extraction and risk-of-bias assessments were conducted by two independent reviewers. We used a random-effects model to pool outcomes. The outcome measures were the spherical equivalents, axial length (AL), anterior chamber depth (ACD), and lens thickness (LT).

Results: Thirteen studies involving 1850 eyes were assessed: 914 in the anti-VEGF drug group, and 936 in the control (laser) group. Children who received anti-VEGF drug treatment had less myopia than those who received laser therapy (mean difference =1.80 diopter, 95% confidence interval =: 0.97 to 2.63, $P < 0.0001$, $I^2 = 78\%$). The AL, ACD, and LT did not reach statistical significance difference between the two groups. The current evidence indicates

that the refractive safety in children with ROP is better for anti-VEGF drug treatment than for laser therapy.

Conclusions*:* This meta-analysis indicates that anti-VEGF drug therapy results in less myopia compared with laser therapy. However, there are relatively few published articles on refractive errors in ROP , and so high-quality and powerful RCTs are needed in the future.

PROSPERO registration number: CRD42020160673

Strengths and limitations of this study

Our meta-analysis adhered to the methodology recommendations of the Cochrane Handbook. We conducted a thorough literature search.

The article describes a review protocol that is formally registered on PROSPERO, and the study was conducted and reported on using rigorous methods following the PRISMA statement.

We included other parameters that may affect the refractive errors in children with ROP in our meta-analysis, such as ACD, LT, and AL

The refractive error measures were from different follow-up time points across studies, this may confound the evaluation of refractive error differences between anti-VEGF and laser

Most of the included studies had an observational design, with only two RCTs being included, The inclusion of more RCTs would have allowed more-reliable conclusions to be drawn.

Introduction

Retinopathy of prematurity (ROP) is a common blinding disease among children in developed countries and is becoming increasingly popular in developing countries.[1] Characterized by retinal ischemia, aberrant angiogenesis, fibrovascular proliferation, and progressive vitreoretinal traction, ROP accounts for 14% and 20% of cases of childhood blindness in the United States and developing countries, respectively.[2]

ROP is a unique retinal vascular proliferative disease occurring in premature and low-birth-weight infants.[3] Retinal vascularization normally occurs at around 12 weeks of gestation and is completed by 36-40 weeks. This prolonged development period means that the retinal system is immature when infants leave the uterus prematurely. The loss of the maternal interaction environment and exposure to high oxygen levels in premature infants can lead to the cessation of retinal vascularization, damage to the capillary endothelium, hypoxia of the retinal blood vessels, and stimulation of fibrovascular tissue proliferation, and might even finally lead to traction retinal detachment.[4]

Laser photocoagulation has previously been the mainstay treatment for ROP. While this intervention is effective and safe, a few defects can remain, such as high myopia, visual field loss, and retinal destruction. An intensive study of ROP found that the levels of vascular endothelial growth factor (VEGF) were markedly elevated in the vitreous of eyes at stage-4 ROP.[5] In a normally developing retina, VEGF promotes the development of blood vessels from the optic nerve to the periphery, whereas the overexpression of VEGF in preterm

infants leads to abnormal vascular proliferation.[6] This situation has prompted researchers to use anti-VEGF drugs to treat ROP. Many studies have shown that the intravitreal injection of anti-VEGF drugs may be an effective clinical intervention for ROP.[7, 8 9] However, the effects of this intervention are relatively short term, while its long-term complications remain unclear, such as postoperative refractive errors. Kang et al.[10] showed that anti-VEGF drugs do not cause refractive errors after ROP treatment, while Kabatas et al.[11] found that effects of the intravitreal injection of anti-VEGF drugs did not differ significantly from those of laser photocoagulation, with both potentially causing refractive errors.

The increasing clinical application of anti-VEGF drugs makes it important to know whether these drugs can also cause refractive errors in children with ROP. Hence, the purpose of the present meta-analysis was to determine the effects of anti-VEGF drugs on the refractive status of ROP compared with laser treatment, and to verify their clinical safety. The outcome measures considered in this study were the spherical equivalents (SE), axial length (AL), anterior chamber depth (ACD), and lens thickness (LT).

Methods

Our study is reported on here in accordance with the PRISMA guidelines for meta-analyses.[12] The study has been registered on PROSPERO (registration number CRD42020160673).

Data sources and search strategy.

From their inceptions to January 2020, we searched the PubMed, Web of Science, EMBASE databases, and the ClinicalTrials.gov website using keywords and medical subject headings. Only studies reported on in English were considered for inclusion. We also searched the reference lists of the selected articles to identify any other relevant articles. The search termsincluded “retinopathy of prematurity,” “prematurity retinopathy,” “retrolental fibroplasia,” “fibroplasia, retrolental,” “ROP,” “anti-VEGF,” “bevacizumab,” “Avastin,” “Lucentis,” “ranibizumab,” “aflibercept,” “anti-vascular endothelial growth factor,” “Mvasi,” and “refractive errors,” “disorders, refractive,” and “ametropias.” The search strategy is detailed in the S1 strategy(online supplementary material).

Study selection and eligibility criteria.

Each study was independently screened by two of the authors (Q.H.K.and M.X.S), with discrepancies between them resolved through discussion with the third author (W.M.). The following inclusion criteria were applied : (1) children who had been clearly diagnosed with ROP, (2) subjects in the intervention group had received an intraocular injection of an anti-VEGF drug that can be used in children with ROP,(3) subjects in the control group had received treatment of the eye using a retinal argon or diode laser., (4)the outcome of interest was the refractive status of the treated children with ROP , including

SE and ocular biometric structural features such as AL, ACD, and LT, and (5) the study design was a randomized controlled trial(RCT) or an observational study. We excluded children with stage-4 ROP,stage-5 ROP, or other eye diseases such as congenital cataract or glaucoma prior to treatment.

Data extraction and quality assessment.

The following information was extracted for the included studies: name of the first author, publication year, sample size, number of eyes, GA (gestational age), BW (birth weight), follow-up time, type of anti-VEGF drug, dose of anti-VEGF drug , and results data (SE, AL, ACD,and LT). When two anti-VEGF drugs had been applied in a study, we extracted the data separately and compared the data with the control group.

We entered the extracted data into an Excel file. Two of the authors (Q.H.K and M.X.S.) assessed the quality of studies using the Newcastle-Ottawa Scales(NOS).[13] The NOS consists of four items for subject selection (maximum 4 points), one item for comparability between groups (maximum 2 points), and three items for outcome measurement (maximum 3 points). The maximum score is therefore 9 points, with studies considered to be of moderate quality having scores of 4–6, and those of high quality having scores of 7–9.[14]

Statistical analysis.

The weighted mean differences (WMDs) with 95% confidence intervals (Cis)

were calculated for continuous variables. Heterogeneity between the included studies was assessed using the I^2 statistic. I^2 values of 25%-50%, 50%-75%,75%-100% were considered to indicate low, moderate, and high heterogeneity,respectively.[15] Due to the possibility of heterogeneity being present between studies, we used a more conservative version of the random-effects model.

A visual funnel plot was used to evaluate publication bias, with an asymmetric plot indicating that publication bias was present. Egger's test was further used to provide accurate assessments of publication bias, with if P< 0.05, considered to indicate some degree of publication bias.

All statistical analyses were performed using RevMan software (version 5.3, Nordic Cochrane Centre) and Stata software (version 12.0, Stata Corporation).

Results

Literature search.

The initial literature search identified 121 records. After screening the titles and Abstracts, 31 potentially eligible studies were assessed for inclusion. After reading the full texts ,13 studies were finally included in the present meta-analysis. The study selection process is illustrated in **Figure 1**.

The 13 selected studies comprised 2 RCTs[16, 17], and 11 observational studies[11, 18-27]. According to the scoring criteria of the NOS, 11 studies were evaluated as being of high quality, while 2 were evaluated as being of moderate quality. The NOS score of the included studies ranged from 6 to 8, with a median of 8. All of

the articles had been published between 2013 and 2019. The sample sizes in the studies ranged from 12 to 397, with a total of 1850 eyes: 914 in the anti-VEGF drug group and 936 in the control group. The included anti-VEGF drugs were bevacizumab and ranibizumab, with one of these drugs administered in 12 studies and 2 drugs administered in 1 study. The dose of anti-VEGF drugs also varied among the included studies, from a minimum of 0.2mg to a maximum of was 1.25mg, with most of the studies using 0.625 mg.

After injecting anti-VEGF drugs, children with ROP were followed regularly for more than 6 months, ranging from 9 months to 5 years. SE values were reported for all of the 13 included studies, while ALs, ACDs, and LTs were reported for 4, 3, and 2 studies, respectively. We presented the main information within the included studies in our meta-analysis. (**Table 1**)

Table 1: Main Characteristics of Studies Included in the Meta-analysis

First author/year	region	Group	patients /eyes(n)	GA(weeks) (mean±SD)	BW(g) (mean±SD)	Follow-up (months)	Type of Anti-VEGF	Anti-VEGF dose(mg)	NOS score
Harder 2013[18]	Germany	Anti-VEGF laser	12/23 13/26	25.20 ± 1.60 25.30± 1.80	622.00 ± 153.00 717.00 ± 197.00	12	bevacizumab	0.375 or 0.625	7
Hwang 2015[19]	American	Anti-VEGF laser	11/22 17/32	NA	668.10 ± 127.30 701.40 ± 118.80	21.7 32.5	bevacizumab	0.625	8
Kabataş 2017[11] ⋆	Turkey	Anti-VEGF laser	12/24 36/72	26.10 ± 2.27 27.70 ± 2.70	841.00 ± 235.00 1,112.00 ± 362.00	18	bevacizumab	0.625	8
Kabataş 2017[11] ⋆	Turkey	Anti-VEGF laser	6/12 36/72	26.00 ± 1.26 27.70 ± 2.70	840.00 ± 177.00 1,112.00 ± 362.00	18	ranibizumab	0.25	8
Kuo 2015[20]	Taiwan	Anti-VEGF laser	15/15 14/14	27.33 ± 2.94 27.43± 2.93	1,079.67 ± 357.48 1,006.79 ± 327.65	3 years of age	bevacizumab	0.5	7
Kang 2019[21]	Korea	Anti-VEGF laser	12/22 15/30	27.40 ± 2.00 34.00 ± 2.90	983.20 ± 265.60 961.00 ± 286.50	4 years of age	bevacizumab ranibizumab	0.625 0.2	7
Isaac 2015[22]	Canada	Anti-VEGF laser	13/23 12/22	25.20 ± 1.40 25.00 ± 1.10	722.00 ± 131.00 674.00 ± 175.00	16.00±6.00 6.00±3.00	bevacizumab	0.625	8
Vujanović2017[23]	Serbia	Anti-VEGF laser	21/42 45/90	29.00 ± 4.00 30.00 ± 4.00	1,175.00 ± 425.00 1,200.00 ± 500.00	9	bevacizumab	0.625	8

Table 1 *(continued)*

First author/year	region	Group	patients /eyes(n)	GA(weeks) (mean±SD)	BW(g) (mean±SD)	Follow-up (months)	Type of Anti-VEGF	Anti-VEGF dose(mg)	NOS score
Gunay 2016[24] ⋆	Turkey	Anti-VEGF laser	55/107 57/113	27.31 ± 2.18 28.23 ± 2.50	1005.29 ±411.19 1119.47 ± 336.96	19.40±6.43 20.68±6.89	bevacizumab	0.625	8
Gunay 2016[24] ⋆	Turkey	Anti-VEGF laser	22/44 57/113	27.95 ± 2.90 28.23 ± 2.50	1195.90 ± 466.98 1119.47 ± 336.96	18.96±4.79 20.68±6.89	ranibizumab	0.25	8
Chen 2019[25]	Taiwan	Anti-VEGF laser	13/25 12/22	26.46 ±1.51 25.50 ±1.24	862.54 ±197.65 815.83 ±151.07	NA	bevacizumab	0.625	7
Lee 2018[26]	Taiwan	Anti-VEGF laser	17/33 13/24	26.60 ± 1.60 26.60 ± 2.50	874.10 ± 228.70 803.10 ± 144.90	> 48	bevacizumab	0.625	6
Roohipoor2018[27]	Iran	Anti-VEGF laser	NA/397 NA/190	27.8	1146	> 12	bevacizumab	0.625	8
Geloneck2014[16]*	American	Anti-VEGF laser	56/110 53/101	24.3	625	2.5 years of age	bevacizumab	0.625	8
O'Keeffe2016[17] *	Irish	Anti-VEGF laser	15/15 15/15	25±1.25	780±135	60	bevacizumab	1.25	6

***:** RCT, Randomized Controlled Trial; NOS: Newcastle-Ottawa Scale; NA: not applicable; GA: gestational age; BW: birth weight;

⋆ : There are two types of Anti-VEGF drugs included in the literature, so the details are listed separately

Main outcomes

Spherical equivalent. The SE values were reported for 914 eyes in the anti-VEGF drug group and 936 eyes in the control group. (**Figure 2**). The SE values were higher in the anti-VEGF drug group than in the control group (MD=1.80 diopter, 95% CI=0.97 to 2.63), with a high heterogeneity (I^2 = 78%). The findings of the subgroup analysis of the SE according to type of article are summarized in **Figure 3.** At the same time, according to different types of anti-VEGF drugs(Online supplementary material S2 forest plot) and different follow-up time (Online supplementary material S3 forest plot), we conducted a subgroup analysis.

Axial length. Three articles [23, 25, 26] reported the AL, with 251 eyes in the anti-VEGF drug group and 362 eyes in the control group. (**Figure 4**). There was no significant difference in the AL between the groups (MD=-0.04mm, 95%=CI: -0.30 to 0.21), and the heterogeneity was low (I^2 = 30%).

Anterior chamber depth. Three articles[23, 25, 26] reported the ACD in children with ROP who were or were not taking anti-VEGF drugs. We found no difference in the ACD between the anti-VEGF drug and control groups(MD=0.19mm; 95% CI=-0.14 to 0.52, I^2 = 85%).(**Figure 5**) There was high heterogeneity(I^2 = 85%), but excluding Vujanović's study in the sensitivity analysis resulted in moderate heterogeneity (MD= 0.39mm; 95% CI=-0.06 to 0.84, I^2 = 64%).

Lens thickness. Two articles[23, 25] reported the LT, which did not differ

significantly between the anti-VEGF drug and laser groups (MD=0.06mm; 95% CI: -0.56 to 0.67, P =0.85), and I^2 was 97%. (online supplementary material: S4 forest plot).

Publication bias

Visual examinations of funnel plots constructed using Stata software. and also statistical calculations using in Egger's test did not reveal any publication bias (P =0.401). (online supplementary material S5 funnel plot)

Discussion

The present meta-analysis identified that 13 previous studies have investigated the association between treatments and refractive errors among children with ROP, and analyzed SE, AL, ACD, and LT. A significant difference in SE was found between the two study groups.,This means that anti-VEGF drug treatment reduces the degree of myopia in children with ROP compared with laser treatment, as consistently found in both the comprehensive and subgroup analyses. However, no significant differences were found in the other variables analyzed in this study.

Meta-analyses of similar subjects have also been reported.[28] The meta-analysis of Tan et al. included 7 articles covering 519 eyes, but this was limited to the anti-VEGF drug bevacizumab. Although the main finding of our meta-analysis was consistent with previous meta-analyses, there are some differences between them. Firstly, our study analyzed the largest amount of data(13 articles covering 1850 eyes) and included some recently published

literature, which increased the statistical power of the analyses. Secondly, in addition to the anti-VEGF drug bevacizumab, another anti-VEGF drug that is commonly used in clinical practice was also included (ranibizumab), which makes the present conclusions closer to clinical reality. Thirdly, we added other ocular parameters to investigate how anti-VEGF drug and laser therapies affect refractive errors: ACD, LT, and AL. A previous study showed that these ocular refractive parameters may be related to myopic adults with ROP,[29] but no evidence was provided for laser treatment and anti-VEGF drug treatment exerting different effects on the refractive status in children with ROP. We, therefore, analyzed these ocular parameters in laser and anti-VEGF drug groups, with the obtained results providing further evidence that anti-VEGF drug treatment is safe for children with ROP.

This meta-analysis of 13 articles synthesized the literature to evaluate the refractive safety of anti-VEGF drugs for children with ROP and has shown that anti-VEGF drug treatment provides better refractive results than does laser treatment. As seen in previous studies, the degree of myopia was reduced more by anti-VEGF drug therapy than by laser treatment in the current study. Most previous studies have quantified refractive errors using SE values, since this parameter is considered the primary measure of such errors, and so we also used this parameter to explore group differences .

Kuo et al[20] and Issec et al.[22] reported that refractive errors did not differ significantly between anti-VEGF drug and laser groups. However, our meta-

analysis found that anti-VEGF drug therapy reduces refractive errors more than does laser treatment. Two factors may explain this difference. (1)both of the previous studies included small samples, and(2) a higher proportion of the children included in the present study had severe ROP. The present findings indicate that anti-VEGF drug therapy may be an alternative to laser therapy for reducing refractive errors in children with ROP. Our subgroup analysis found that anti-VEGF drug therapy exerted better effects on refractive errors than did laser therapy, based on findings in both RCTs and observational studies.

Laser therapy has been considered the first choice of treatment for ROP and has well-established safety and efficacy. However, this approach results in the retina being permanently cauterized, leading to inadequate vascularization and the risk of visual field loss, high myopia, and cataracts. Regarding refraction, it has also been reported that laser treatment may be a risk factor for refractive errors in children with ROP.[30] Therefore, the impact of future damage to the refractive status that may result from laser treatment needs to be considered when treating children with ROP, indicating the need to find a treatment method with increased effectiveness and safety. A previous in-depth study of the ROP mechanism found that the intraocular injection of an anti-VEGF drug may be a good alternative to laser treatment.[22] The intraocular injection of anti-VEGF drugs has the advantages of less trauma and pain and involving an easy procedure, which has resulted in it being increasingly used by a large number of clinicians. This situation makes it essential to clarify the safety regarding

refractive errors as soon as possible, and the present meta-analysis has provided good evidence for the refractive safety of anti-VEGF drugs.

Changes in the biometric structure of the eye—such as in ACD, LT, AL, corneal curvature, and corneal diameter—may be related to increased refractive errors.[31-33] We, therefore, regard it as essential to consider the above indicators of ocular biometric structure when verifying the refractive status of children with ROP. Although there have been previous meta-analyses of refractive outcomes after treatment of ROP with anti-VEGF drug therapy, none of these meta-analyses explored the relationship between refractive outcomes and the biometric structure of the eye when comparing anti-VEGF drug and laser therapies. Our study found no significant intergroup differences in these parameters. There is also considerable debate about whether anti-VEGF drug treatment of ROP will induce changes in ocular parameters. Lee et al found that AL did not differ among different treatment groups. Gunay et al[34] reported that in children who receive anti-VEGF drug therapy, the AL might be related to the development of myopia and is not related to the ACD or LT. The BEAT-ROP believes that anti-VEGF drug treatment may facilitate the continuation of the local growth factor expression and signaling pathways, allowing the anterior segment to develop normally[16]. The small number of articles that have reported on the ocular biometric structure makes it difficult to draw definitive conclusions, and so more high-quality RCTs are needed to verify the impact of anti-VEGF drugs on the ocular biometric structure.

We consider that future research should focus on two main aspects. Firstly, there is no unified standard for the optimal dose of anti-VEGF drugs to use in the treatment of ROP. Most clinical applications used doses are half of the adults, but if other doses of anti-VEGF treatment of ROP affect the result, we do not know, so in the future, a clear plan for the dose of anti-VEGF needs to be proposed. Secondly, there is no clear standard for the follow-up time of children with ROP. The conclusions that may be drawn lack credibility if the follow-up time is too short, and so the most-appropriate follow-up time of children after treatment with anti-VEGF drugs also needs to be determined.

The first strength of our meta-analysis is that it adhered to the methodology recommendations of the Cochrane Handbook, and included conducting a thorough literature search. Secondly, this meta-analysis has a formally registered review protocol on PROSPERO, and our investigations were conducted and reported with rigorous methods following the PRISMA statement. Thirdly, our meta-analysis included other parameters that may affect the refractive errors in children with ROP, such as ACD, LT, and AL. The results further strengthen the evidence for the safety of anti-VEGF drugs in children with ROP. However, our study also had certain limitations. First, the refractive error measures were from different follow-up time points across studies, this may confound the evaluation of refractive error differences between anti-VEGF and laser. Second, most of the included studies had an observational design, with only two RCTs being included, The inclusion of more RCTs would have

allowed more-reliable conclusions to be drawn.

Conclusions

In conclusion, the present meta-analysis has shown that anti-VEGF drug therapy reduces the degree of myopia more effectively than does laser treatment. The current evidence indicates that anti-VEGF drug treatment has better refractive safety than laser therapy for children with ROP. Since intraocular injections of angiogenesis factor inhibitors are increasingly being applied, more high-quality RCTs are required.

Footnotes

Contributors: Qi-Hang Kong and Xue-Song Mi conceived the idea of the article, Qi-Hang Kong and Xue-Song Mi did the literature search. Qi-Hang Kong, Xue-Song Mi, and Wai-kit Ming undertook the data acquisition and analysis. Qi-Hang Kong carried out the manuscript preparation. Xue-Song Mi and Wai-kit Ming were responsible for the revision of the manuscript. All authors have read and approved the final manuscript.

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Provenance and peer review: Not commissioned; externally peer-reviewed.

Data sharing statement: All data analyzed in this study are included in the article and its supplementary files.

Patient and Public Involvement: No patient involved

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Figure legends

Figure 1 Selection of studies for the meta-analysis

Figure 2 Forest plot of spherical equivalent.

Figure 3 Forest plot of the effect anti-VEGF therapy on spherical equivalent, according to the types of article included

Figure 4 Forest plot of axial length (AL)

Figure 5 Forest plot of anterior chamber depth (ACD).

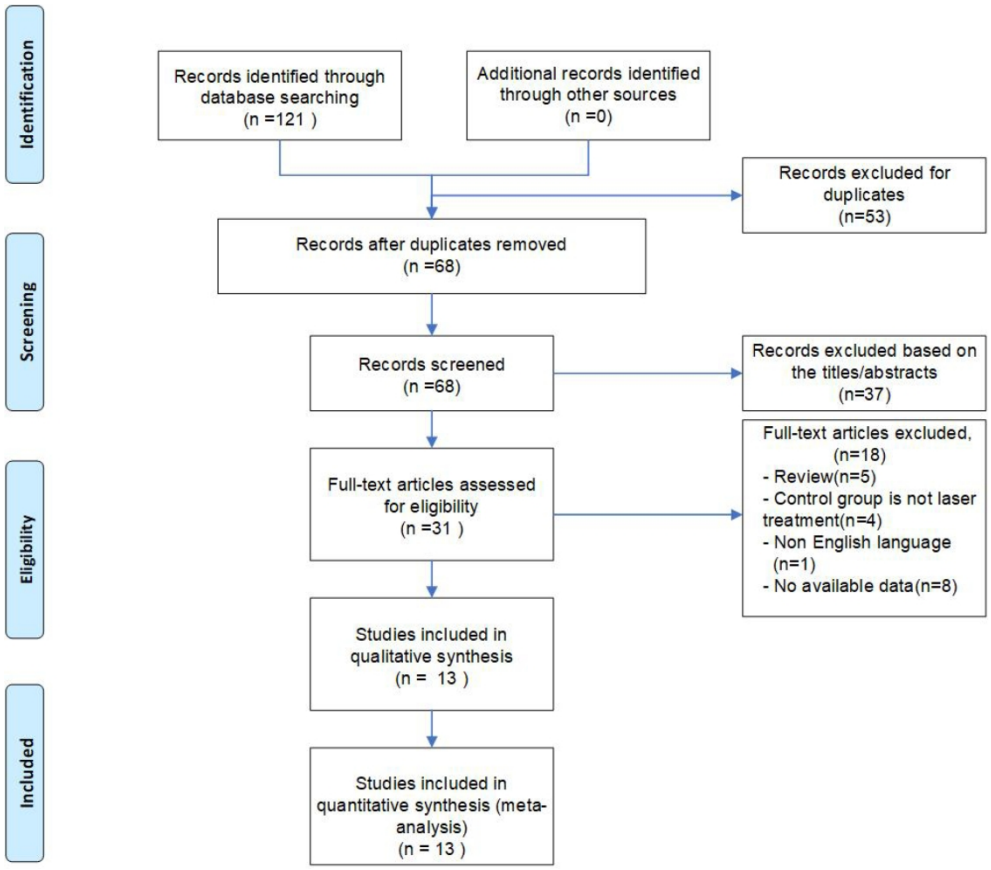

Identification
Screening
Eligibility
Included
Records identified through database searching (n =121)
Additional records identified through other sources (n =0)
Records excluded for duplicates (n=53)
Records after duplicates removed (n =68)
Records screened (n =68)
Records excluded based on the titles/abstracts (n=37)
Full-text articles assessed for eligibility (n =31)
Full-text articles excluded, (n=18)
- Review(n=5)
- Control group is not laser treatment(n=4)
- Non English language (n=1)
- No available data(n=8)
Studies included in qualitative synthesis (n = 13)
Studies included in quantitative synthesis (meta-analysis) (n = 13)

Figure 1

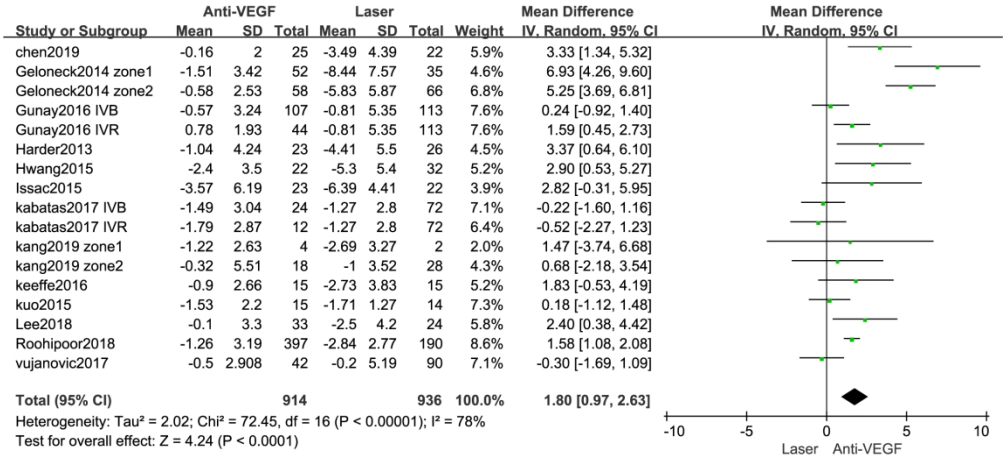

Anti-VEGF
Laser
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
chen2019 -0.16 2 25 -3.49 4.39 22 5.9% 3.33 [1.34, 5.32]
Geloneck2014 zone1 -1.51 3.42 52 -8.44 7.57 35 4.6% 6.93 [4.26, 9.60]
Geloneck2014 zone2 -0.58 2.53 58 -5.83 5.87 66 6.8% 5.25 [3.69, 6.81]
Gunay2016 IVB -0.57 3.24 107 -0.81 5.35 113 7.6% 0.24 [-0.92, 1.40]
Gunay2016 IVR 0.78 1.93 44 -0.81 5.35 113 7.6% 1.59 [0.45, 2.73]
Harder2013 -1.04 4.24 23 -4.41 5.5 26 4.5% 3.37 [0.64, 6.10]
Hwang2015 -2.4 3.5 22 -5.3 5.4 32 5.2% 2.90 [0.53, 5.27]
Issac2015 -3.57 6.19 23 -6.39 4.41 22 3.9% 2.82 [-0.31, 5.95]
kabatas2017 IVB -1.49 3.04 24 -1.27 2.8 72 7.1% -0.22 [-1.60, 1.16]
kabatas2017 IVR -1.79 2.87 12 -1.27 2.8 72 6.4% -0.52 [-2.27, 1.23]
kang2019 zone1 -1.22 2.63 4 -2.69 3.27 2 2.0% 1.47 [-3.74, 6.68]
kang2019 zone2 -0.32 5.51 18 -1 3.52 28 4.3% 0.68 [-2.18, 3.54]
keeffe2016 -0.9 2.66 15 -2.73 3.83 15 5.2% 1.83 [-0.53, 4.19]
kuo2015 -1.53 2.2 15 -1.71 1.27 14 7.3% 0.18 [-1.12, 1.48]
Lee2018 -0.1 3.3 33 -2.5 4.2 24 5.8% 2.40 [0.38, 4.42]
Roohipoor2018 -1.26 3.19 397 -2.84 2.77 190 8.6% 1.58 [1.08, 2.08]
vujanovic2017 -0.5 2.908 42 -0.2 5.19 90 7.1% -0.30 [-1.69, 1.09]
Total (95% CI) 914 936 100.0% 1.80 [0.97, 2.63]
Heterogeneity: Tau² = 2.02; Chi² = 72.45, df = 16 (P < 0.00001); I² = 78%
Test for overall effect: Z = 4.24 (P < 0.0001)
-10
-5
0
5
10
Laser
Anti-VEGF

Figure 2

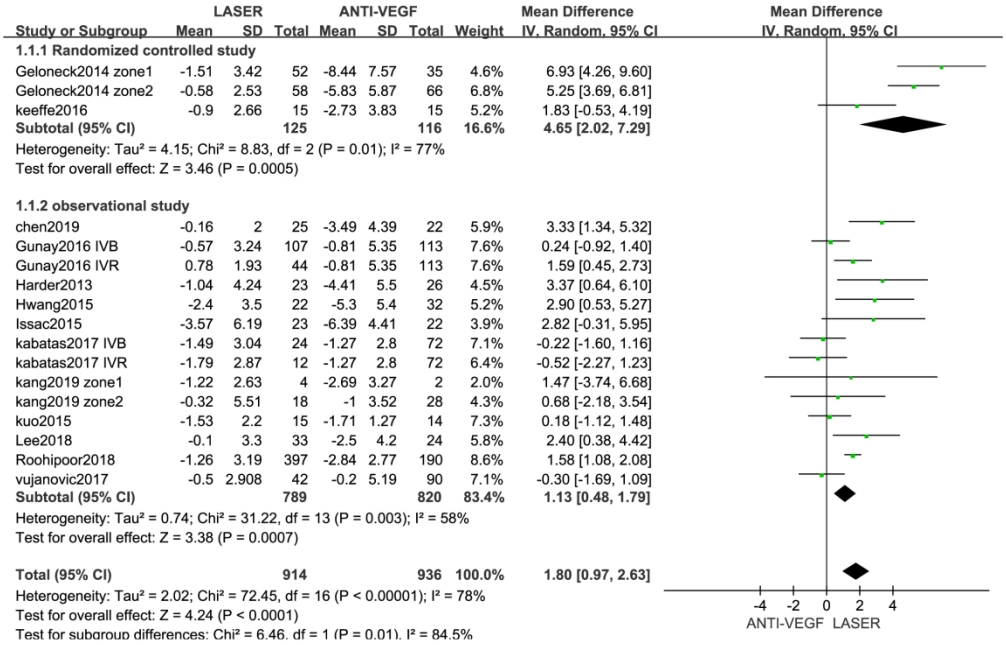

LASER
ANTI-VEGF
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
1.1.1 Randomized controlled study
Geloneck2014 zone1 -1.51 3.42 52 -8.44 7.57 35 4.6% 6.93 [4.26, 9.60]
Geloneck2014 zone2 -0.58 2.53 58 -5.83 5.87 66 6.8% 5.25 [3.69, 6.81]
keeffe2016 -0.9 2.66 15 -2.73 3.83 15 5.2% 1.83 [-0.53, 4.19]
Subtotal (95% CI) 125 116 16.6% 4.65 [2.02, 7.29]
Heterogeneity: Tau² = 4.15; Chi² = 8.83, df = 2 (P = 0.01); I² = 77%
Test for overall effect: Z = 3.46 (P = 0.0005)
1.1.2 observational study
chen2019 -0.16 2 25 -3.49 4.39 22 5.9% 3.33 [1.34, 5.32]
Gunay2016 IVB -0.57 3.24 107 -0.81 5.35 113 7.6% 0.24 [-0.92, 1.40]
Gunay2016 IVR 0.78 1.93 44 -0.81 5.35 113 7.6% 1.59 [0.45, 2.73]
Harder2013 -1.04 4.24 23 -4.41 5.5 26 4.5% 3.37 [0.64, 6.10]
Hwang2015 -2.4 3.5 22 -5.3 5.4 32 5.2% 2.90 [0.53, 5.27]
Issac2015 -3.57 6.19 23 -6.39 4.41 22 3.9% 2.82 [-0.31, 5.95]
kabatas2017 IVB -1.49 3.04 24 -1.27 2.8 72 7.1% -0.22 [-1.60, 1.16]
kabatas2017 IVR -1.79 2.87 12 -1.27 2.8 72 6.4% -0.52 [-2.27, 1.23]
kang2019 zone1 -1.22 2.63 4 -2.69 3.27 2 2.0% 1.47 [-3.74, 6.68]
kang2019 zone2 -0.32 5.51 18 -1 3.52 28 4.3% 0.68 [-2.18, 3.54]
kuo2015 -1.53 2.2 15 -1.71 1.27 14 7.3% 0.18 [-1.12, 1.48]
Lee2018 -0.1 3.3 33 -2.5 4.2 24 5.8% 2.40 [0.38, 4.42]
Roohipoor2018 -1.26 3.19 397 -2.84 2.77 190 8.6% 1.58 [1.08, 2.08]
vujanovic2017 -0.5 2.908 42 -0.2 5.19 90 7.1% -0.30 [-1.69, 1.09]
Subtotal (95% CI) 789 820 83.4% 1.13 [0.48, 1.79]
Heterogeneity: Tau² = 0.74; Chi² = 31.22, df = 13 (P = 0.003); I² = 58%
Test for overall effect: Z = 3.38 (P = 0.0007)
Total (95% CI) 914 936 100.0% 1.80 [0.97, 2.63]
Heterogeneity: Tau² = 2.02; Chi² = 72.45, df = 16 (P < 0.00001); I² = 78%
Test for overall effect: Z = 4.24 (P < 0.0001)
Test for subgroup differences: Chi² = 6.46, df = 1 (P = 0.01), I² = 84.5%
-4 -2 0 2 4
ANTI-VEGF LASER

Figure 3

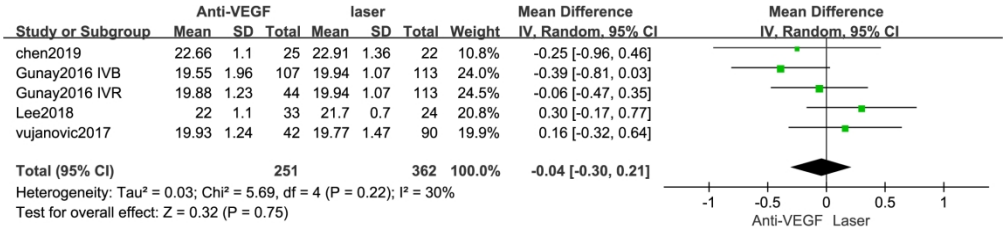

Anti-VEGF
laser
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
chen2019 22.66 1.1 25 22.91 1.36 22 10.8% -0.25 [-0.96, 0.46]
Gunay2016 IVB 19.55 1.96 107 19.94 1.07 113 24.0% -0.39 [-0.81, 0.03]
Gunay2016 IVR 19.88 1.23 44 19.94 1.07 113 24.5% -0.06 [-0.47, 0.35]
Lee2018 22 1.1 33 21.7 0.7 24 20.8% 0.30 [-0.17, 0.77]
vujanovic2017 19.93 1.24 42 19.77 1.47 90 19.9% 0.16 [-0.32, 0.64]
Total (95% CI) 251 362 100.0% -0.04 [-0.30, 0.21]
Heterogeneity: Tau² = 0.03; Chi² = 5.69, df = 4 (P = 0.22); I² = 30%
Test for overall effect: Z = 0.32 (P = 0.75)
-1
-0.5
0
0.5
1
Anti-VEGF
Laser

Figure 4

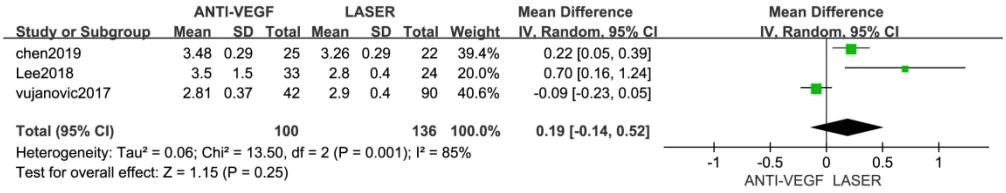

ANTI-VEGF
LASER
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
chen2019 3.48 0.29 25 3.26 0.29 22 39.4% 0.22 [0.05, 0.39]
Lee2018 3.5 1.5 33 2.8 0.4 24 20.0% 0.70 [0.16, 1.24]
vujanovic2017 2.81 0.37 42 2.9 0.4 90 40.6% -0.09 [-0.23, 0.05]
Total (95% CI) 100 136 100.0% 0.19 [-0.14, 0.52]
Heterogeneity: Tau² = 0.06; Chi² = 13.50, df = 2 (P = 0.001); I² = 85%
Test for overall effect: Z = 1.15 (P = 0.25)
-1
-0.5
0
0.5
1
ANTI-VEGF
LASER

Figure 5

S1 strategy.

Detailed search strategy for PubMed

1. Retinopathy of Prematurity[MeSH]

2. Prematurity Retinopath*[Tiab] OR Retrolental Fibroplasia*[Tiab] OR Fibroplasia* Retrolental[Tiab]

3.1 OR 2

4. Anti-VEGF[MeSH]

5. Mvasi[Tiab] OR Avastin[Tiab] OR Ranibizumab[Tiab] OR aflibercept[Tiab] OR Anti-vascular endothelial growth factor[Tiab]

6.4 OR 5

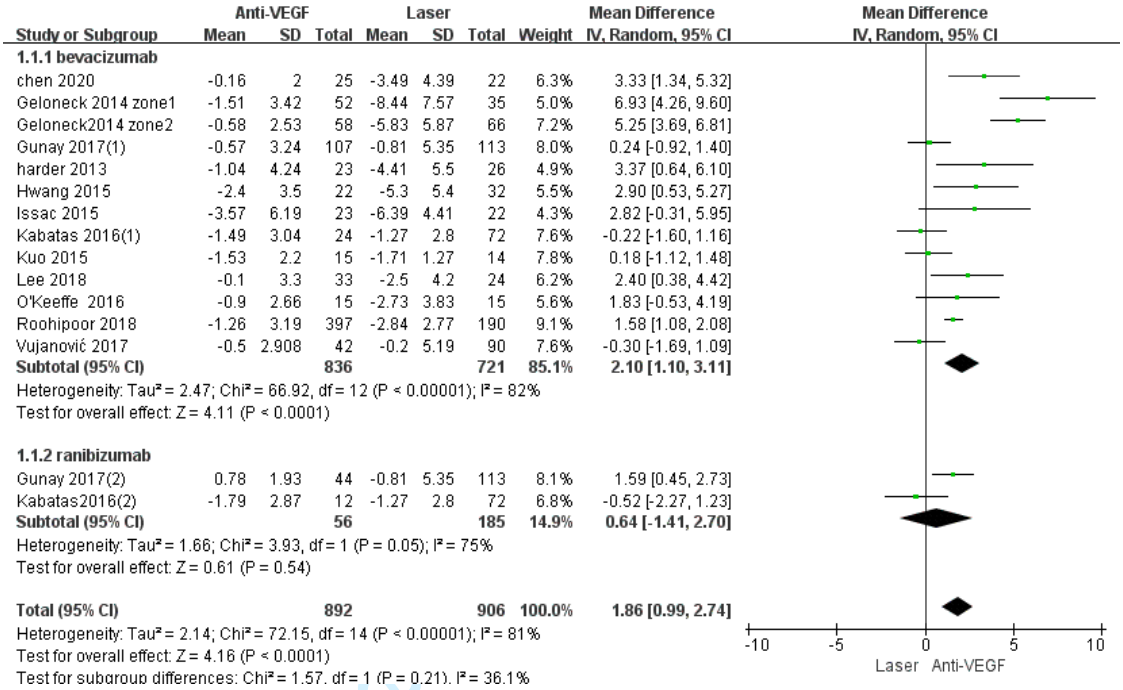
7. Error*,Refractive[MeSH]

8. Error*,Refractive[Tiab] OR Refractive Error*[Tiab] OR Disorder*,Refractive[Tiab] OR Ametropia[Tiab]

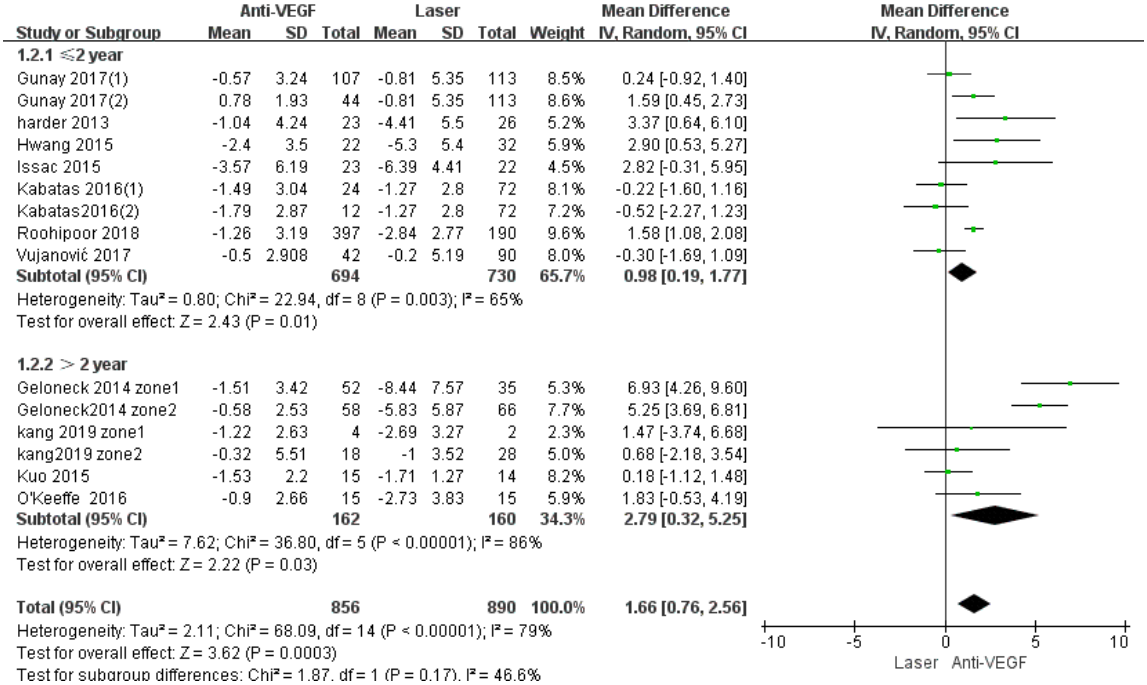
9.7 OR 8

10 3 AND 6 AND 9

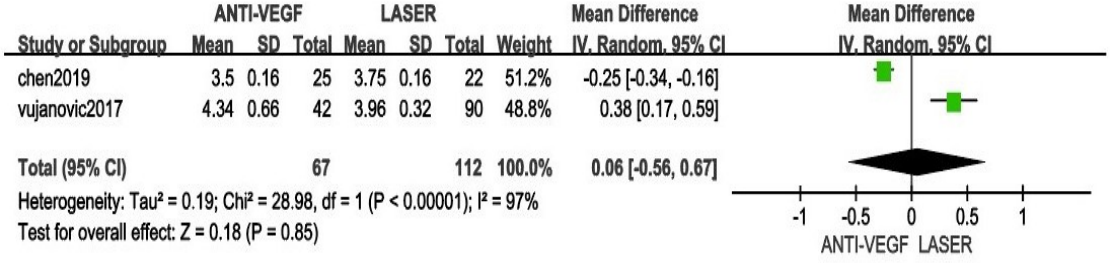
S2 forest plot : Forest plot of the effect of different anti-VEGF drugs on spherical equivalent.



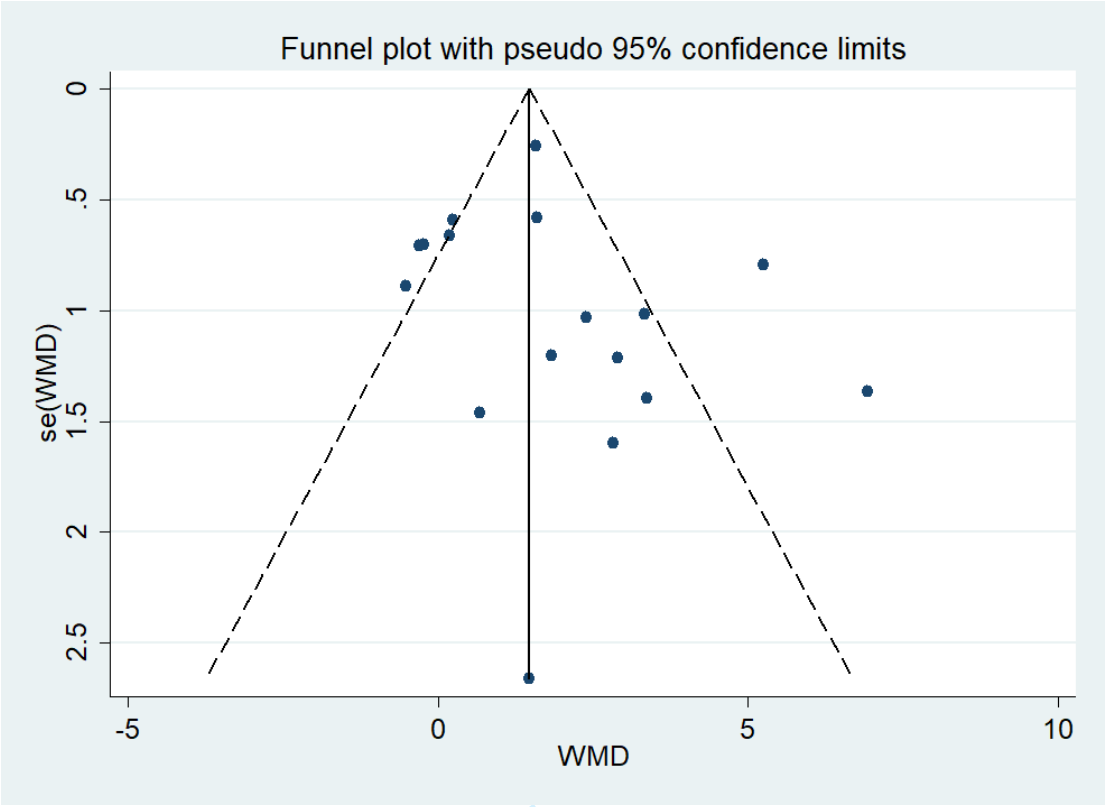
S3 forest plot : Forest plot of the influence of different follow-up time on spherical equivalent.



S4 forest plot :Forest plot of lens thickness (LT).



S5 funnel plot: Publication bias was evaluated by the funnel plot.



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3,4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4,5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7,8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6,7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6(S1 strategy)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7,8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7,8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8,9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	13
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10(Table1)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13(S2 funnel plot)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18,19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19

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