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REVIEW

Safety and Efficacy of Combination Therapy with Anti-Vascular Endothelial Growth Factor and Laser for Retinopathy of Prematurity: A Systematic Review and Meta-Analysis

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Aim: This systematic review and meta-analysis aimed to evaluate the safety and efficacy of combined laser and anti-VEGF therapy for (retinopathy of prematurity ROP), focusing on both structural and functional outcomes.

Methods: A comprehensive search was conducted in multiple databases to identify randomized controlled trials (RCTs) that investigated combination therapy for ROP. The PRISMA guidelines were followed. Data were extracted and analyzed using risk ratios and 95% confidence intervals (CIs). The Cochrane Risk of Bias tool was used to assess the risk of bias.

Results: Three RCTs involving a total of 162 premature infants were included in the meta-analysis. Combination therapy of anti-VEGF and laser photocoagulation was compared with other interventions. The pooled analysis of favorable structural outcomes did not show a statistically significant difference between combination therapy with anti-VEGFs and laser therapy compared to the interventions in the control groups (P=0.25). The incidence of adverse events was comparable between the combination therapy group and other intervention groups.

Conclusion: This systematic review and meta-analysis suggest that risk ratio of combination therapy with anti-VEGF and laser for ROP is associated with favorable outcomes, albeit insignificant. The safety profile of combination therapy appears to be similar to other interventions. However, due to the limited number of included studies, further research is needed.

Keywords: neonatal retinal disease, angiogenesis inhibitors, retinal photocoagulation, premature infant eye health

Introduction

Retinopathy of prematurity (ROP), a condition that affects mainly premature infants, is known to be a leading cause of visual impairment and blindness in children, globally.[1–3] Preterm infants will have underdeveloped retinal vasculature, as these vessels are expected to fully vascularize the retina at 36 to 40 weeks of gestational age.[4,5] Moreover, avascular retinal areas are at higher risk of fostering abnormal vessels mainly driven by excess oxygen exposure after birth.[6] These abnormal vessels can regress without complications, however, some cases may end up with tractional membranes leading to retinal detachment. Factors like lower birth weight, oxygen level fluctuations, acidosis, intraventricular hemorrhage, anemia, hypercapnia, and chronic lung disease are contributors to ROP development.[5,6]

While most ROP cases regress spontaneously, serious complications necessitate immediate intervention.[7,8] Laser photocoagulation is commonly used to ablate the peripheral avascular zone in ROP treatment.[1,2,7] The role of vascular endothelial growth factor (VEGF) in ROP pathogenesis is well-documented, mainly influencing vascular permeability

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and neovascularization.[9] The introduction of intravitreal anti-VEGF therapy in 2007 was a significant milestone in retinal vascular diseases treatment as studies consistently report therapeutic benefits of anti-VEGF agents in managing ROP, highlighting their potential to mitigate ROP progression and improve long-term visual outcomes.[10,11]

Laser therapy significantly reduces unfavorable structural outcomes in ROP patients.[12,13] However, it is linked with some adverse events, including visual field reduction, laser-induced myopia, choroidal bleeding, exudative retinal detachment, and anterior segment ischemia complications (cataracts, phthisis, and pupillary membranes).[14–19] Conversely, the adverse effects of anti-VEGF agents in ROP are not fully understood. Concerns about cerebrovascular side effects following Ranibizumab therapy in adults exist, but bevacizumab is the most used anti-VEGF agent, off-label. Uncertainty remains about the risk of systemic adverse events.[9,20] Compared to laser therapy, anti-VEGF agents offer advantages like ease and rapidity of administration under topical anesthesia, lower rates of severe myopia post-treatment, and less visual field reduction.[14,15,21]

Previous studies have reported promising results and fewer disadvantages of combining laser therapy with anti-VEGF agents for the treatment of retinopathy of prematurity (ROP).[11,12,22,23] Building upon this evidence, our study is motivated by the potential benefits of combining these modalities in managing ROP. This combined approach holds promise for faster regression of neovascularization and may reduce the need for retreatment.[24–26] By concurrently targeting different aspects of ROP pathology, such as avascular retina and fibrovascular proliferation, Combined therapy might reduce the likelihood of complications related to the treatment and is beneficial as it is offering a personalized approach. However, there are still gaps in the literature regarding the overall safety and efficacy of this combination therapy, underscoring the need for further research in this area. Therefore, the aim of our meta-analysis is to evaluate the efficacy of combined laser and anti-VEGF therapy for ROP, focusing on both structural and functional outcomes, and to assess the safety of this approach.

Materials and Methods

Methods

This study was registered in PROSPERO (CRD42023477452) prior to conducting the systematic search, and we have followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist to report the findings in this article (The PRISMA 2020 statement).[27]

Eligibility Criteria

This study included all randomized controlled trials (RCTs) that focused on preterm infants with type 1 retinopathy of prematurity (ROP). Type 1 ROP included specific criteria such as Zone I any stage with plus disease, Zone I stage 3 ROP with or without plus disease, and Zone II stage 2 or 3 ROP with plus disease. Infants with more advanced stages of ROP (stage 4 or higher) at the time of enrollment were excluded from the analysis. The criteria specified that the infants should have been born before 37 weeks' gestation.[13]

Search Strategy and Study Selection

A comprehensive electronic search was conducted in three databases: PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and Directory of Open Access Journals (DOAJ). Additionally, the clinicaltrials.gov register was searched for relevant studies. The search strategy used various key elements related to the population (retinopathy of prematurity or ROP), intervention (anti-vascular endothelial growth factor medications and laser therapy), and outcome (safety, adverse events, complications, efficacy, effectiveness, visual acuity, retinal detachment). Medical subheading (MeSH) terms and limiters specific to each database were incorporated into the search strategy.

Data Extraction and Analysis

Data extraction was conducted using a standardized Excel sheet. Two authors independently extracted the relevant data, and any discrepancies were resolved through consensus or the involvement of a third author. The extracted data included primary and secondary outcome measures, study characteristics (such as study design, country, first author, type of intervention(s), number of participants, length of follow-up, and randomization), and information related to the risk of bias assessment. The collected data

were reported in a meta-analysis using risk ratios and 95% confidence intervals (CIs). The random-effects model was chosen to combine the results of individual studies, and the inverse variance method was used for the meta-analysis. Forest plots were examined to assess the heterogeneity between trial results. The I2 statistic was employed to quantify the amount of variation between studies and measure the inconsistency of the findings.

Certainty of Evidence

The Cochrane Risk of Bias tool was used to assess the risk of bias and methodological quality of the included studies.[28] This tool evaluates multiple domains that can contribute to bias, including selection bias (sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective reporting). By assessing these domains, the reviewers can determine the overall risk of bias in the included studies and evaluate the quality of evidence presented in the systematic review and meta-analysis.

Moreover, we evaluated the quality of evidence for each outcome using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria.[24] The GRADE tool, recommended by Cochrane, was utilized to assess the quality of evidence and determine the strength of recommendations in the studies included in the meta-analysis.[25] This assessment took into account factors such as study design, consistency, relevance, variability, precision, publication bias, and other characteristics reported in the papers included in this systematic review. Based on this evaluation, the quality of evidence was categorized as high, moderate, low, or very low.[22,23]

Results

Study Selection Process and Characteristics of the Included Studies

The electronic search process yielded a total of 377 records after removing duplicates. Two authors independently screened all the retrieved records, and any discrepancies were resolved through consensus or with the involvement of a third author. Out of these, the full texts of seven records were assessed for eligibility, and three of them were included in this review. Figure 1 provides a detailed overview of the study selection process.[24–26]

Among the three included studies, one compared combination therapy of diode laser photocoagulation and adjuvant intravitreal pegaptanib or bevacizumab versus cryotherapy combined with conventional laser photocoagulation or laser therapy alone.[24] Another study compared early laser therapy plus intravitreal Ranibizumab with delayed laser and intravitreal Ranibizumab.[25] The third study compared laser monotherapy with combination therapy of intravitreal bevacizumab and laser therapy.[26] In terms of ROP classifications, one trial specifically included patients with zone II ROP,[26] while the remaining two studies included patients with either zone I or II ROP.[24,25]

The included studies enrolled a total of 162 premature infants (321 eyes), who were randomly allocated to receive combination therapy of anti–vascular endothelial growth factor and laser photocoagulation (83 infants/164 eyes) or other interventions (79 infants/157 eyes). Please refer to Tables 1–4 for more details.

Risk of Bias in the Included Studies

Two authors independently evaluated the risk of bias, and any discrepancies were resolved through consensus or with the assistance of a third author. The assessment of risk of bias is presented in Figure 2. In terms of selection bias and performance bias, two studies had an unclear risk of bias in this domain,[24,25] while the third study had a low risk of bias.[26] Additionally, all three studies had an unclear risk of bias in the detection bias domain. Regarding attrition bias, all studies had a low risk of bias. In the reporting bias domain, two studies had a low risk of bias,[25,26] while the third study had an unclear risk of bias.[24] Overall, two of the included studies had an unclear risk of bias,[24,25] and the third study had a low risk of bias.[26]

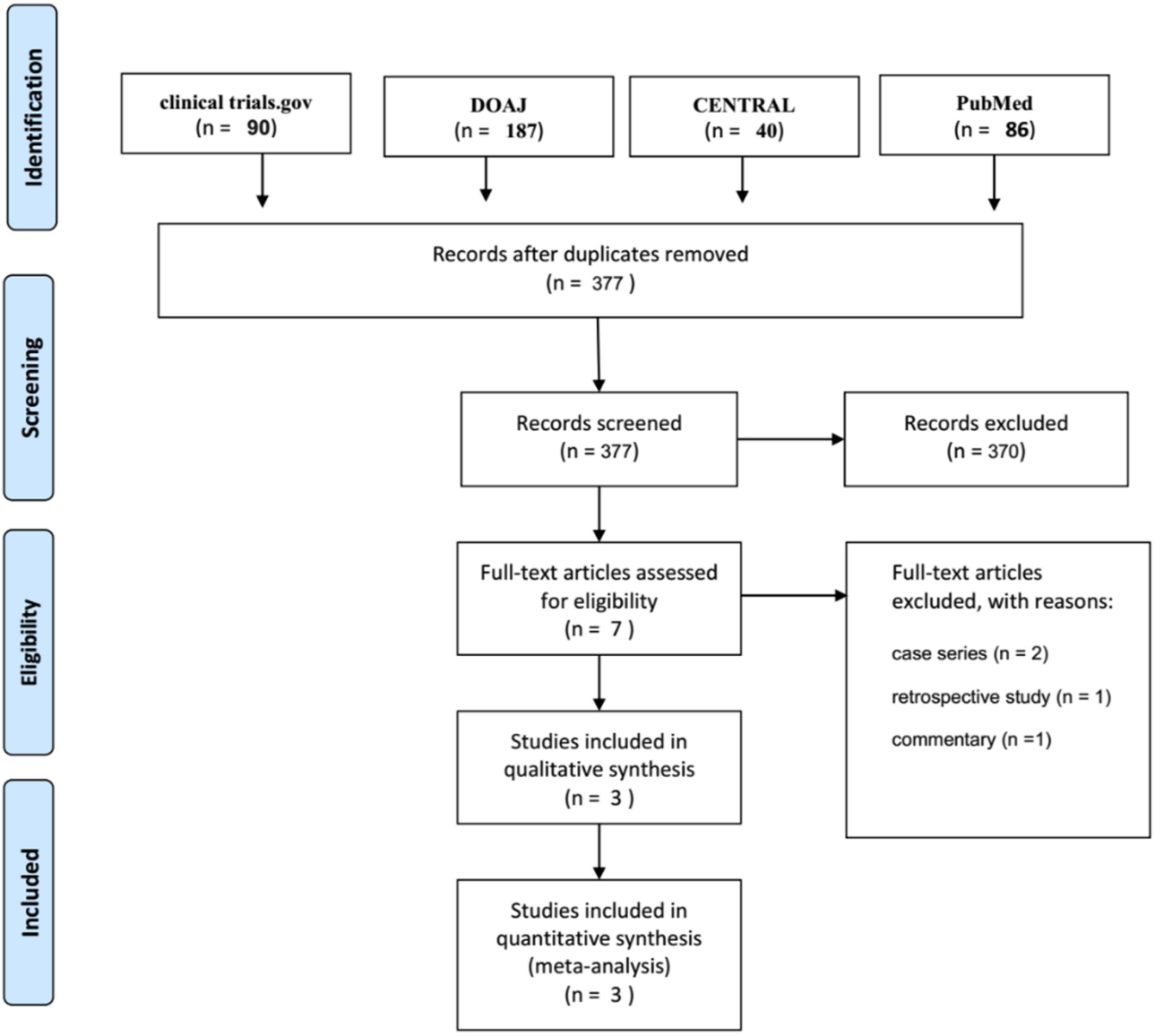

Figure 1 PRISMA flow chart of the study selection process.

Efficacy

Structural Outcome

Three studies were included in the efficacy analysis.[24–26] Pooled analysis of the favorable structural outcome revealed that no statistically significant difference was found between the combination therapy with anti-VEGFs and laser therapy in comparison with the interventions in the control groups (P=0.25) However, the risk ratio for having favorable outcome was more favoring the patients in the combination therapy group, 1.12 (95% CI: 0.92–1.37), Figure 3 illustrates the results of the pooled analysis. The heterogeneity among the included studies was high (P=0.002; I2 =85%).

Functional Outcome

None of the included studies reported the results of functional outcomes such as the rate of severe visual impairment, blindness, and nystagmus. However, one study reported that the rate of refractive error at six months was in 10 eyes in the deferred laser group compared to 15 eyes in the early laser plus intravitreal Ranibizumab (IVR), the mean Spherical equivalent (SE) was 0.94 in the early laser group compared to -0.05 in the deferred laser group.[25]

Table 1 Characteristics of Autrata et al Study

Autrata 2012[24]	
Study design	Single center Randomized controlled trial, conducted in a university hospital, Brno, Czech Republic.
Participants	Preterm infants, with Zone I and posterior zone II ROP, 87 participants (eyes= 174).
Interventions	• Intervention group (46 participants / 92 eyes): received diode laser therapy (810 nm) plus adjuvant intravitreal pegaptanib [0.3 mg] (60 eyes) or intravitreal bevacizumab [0.625 mg/ 0.025 mL] (32 eyes). • Control group (41 participants/ 82 eyes): received Classical photocoagulation with or without cryotherapy. In the case of combined treatment, a diode laser was applied to the central parts of the avascular retina, and cryotherapy peripherally.
Outcomes	• Primary outcomes: Success and failure of the treatment. Success of the treatment was defined as absence of recurrence of stage 3+ ROP in one or both eyes in zone I or posterior zone II within 55 weeks of gestational age. Failure was defined as recurrence of neovascularization in one or both eyes with the need to repeat the treatment. • Secondary outcomes: time to achieve regression – disappearance of "plus disease" symptoms, completion of normal peripheral vascularization, length of hospital stay in the neonatal unit, rate of Perioperative complications.

Table 2 Characteristics of Gangwe et al Study

Gangwe 2021[25]	
Study design	Single center Randomized controlled trial, conducted in India.
Participants	Preterm infants diagnosed with Aggressive posterior retinopathy of prematurity, in zone I and II, 32 infants (63 eyes)
Interventions	• Intervention group (16 infants/ 30 eyes): received intravitreal Ranibizumab (IVR) (0.25mg in 0.025mL) and early laser (at one week after receiving IVR). • Control group (16 infants/31 eyes): received intravitreal Ranibizumab (IVR) (0.25mg in 0.025mL) and deferred laser (at six weeks after receiving IVR).
Outcomes	• Primary outcomes: comparing the structural outcomes (favorable or unfavorable) between the groups. A favorable outcome was defined as regression of the disease completely, characterized by disappearance of peripheral retinopathy and plus disease. The unfavorable outcome was defined as the existence of active disease characterized by recurrence or persistence of plus disease. Additional unfavorable outcomes also included; pre-retinal hemorrhage obscuring macula, tractional retinal detachment, and regression with cicatricial sequalae. • Secondary outcomes: refractive error (as spherical equivalent (SE), and number of laser spots.

Table 3 Characteristics of Namvar et al Study

Namvar 2022[26]	
Study design	Double-blinded randomized clinical trial, conducted in Iran.
Participants	Preterm infants, diagnosed with type 1 zone II ROP, 43 infants (86 eyes).
Interventions	• Intervention group (21 infants/ 42 eyes): Combination of intravitreal Bevacizumab (0.625 mg; 0.025 mL) and laser ablation (laser diode Photocoagulation, 810-nm). • Control group (22 infants/ 44 eyes): Monotherapy with laser ablation (laser diode Photocoagulation, 810-nm)
Outcomes	• Primary outcomes: regression of time of plus disease and extraretinal fibrovascular proliferation, and rate of complications. • Secondary outcomes: reactivation, Progression, retreatment, Intraocular pressure, and number of laser spots.

Safety Profile and Recurrence Rate

Regarding adverse events, Namvar et al stated that no complications were recorded among the two arms of the trial.[26] Moreover, Autrata et al reported that retinal hemorrhage after photocoagulation occurred in 8% of eyes in the combination therapy group and 11% of eyes in the laser group, however this difference was not statistically significant (P = 0.358). No ocular or systemic complications or side effects of intravitreal injection of pegaptanib or bevacizumab.[24]

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Table 4 Summery of the Included Studies

	Autrata 2012[24]	**Gangwe 2021**[25]	**Namvar 2022**[26]
Treatment group	ROP TYPE I	A-ROP	ROP TYPE I
	Pentaganib or bevacizumab + laser	Ranibizumab + laser	Bevacizumab + laser
Zone	I,II	I	II
Control	Group Laser + cryo	Ranibizumab + laser 6th week	Laser

In terms of the recurrence of ROP after treatment, one study reported that combination therapy resulted in a faster disappearance of signs of ROP and a quicker restoration of normal peripheral retinal vascularity compared to the control group.[24] Another study found that recurrence of plus disease occurred in both groups: the deferred laser and the early laser groups.[25]

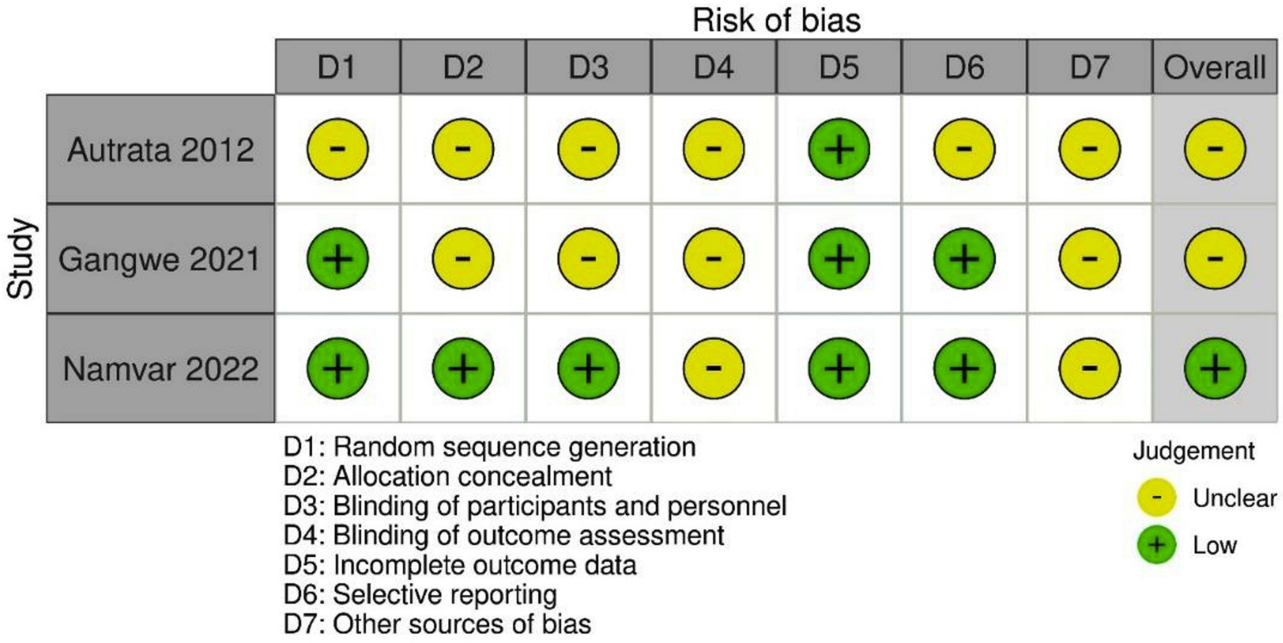

Figure 2 Risk of Bias assessment of the included studies.

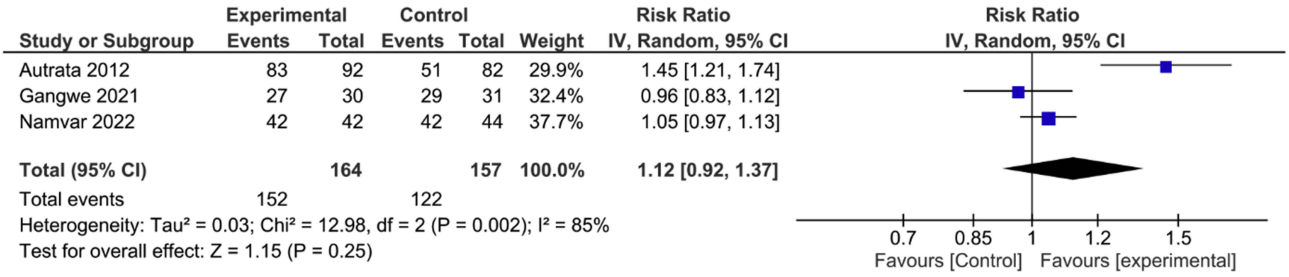

Figure 3 Forest plot of the pooled analysis of favorable structural outcomes of combination therapy with anti-VGEFs and laser therapy versus control interventions for the treatment of ROP.

Discussion

The aim of this meta-analysis was to evaluate the efficacy of combination therapy with laser and anti-VEGF agents for the treatment of ROP. Laser therapy has long been the standard treatment for ROP by ablating the peripheral avascular retina. It takes around two weeks for laser ablation to cease the release of VEGF, and, as a result, halt retinal neovascularization process.[5,11,26] On the other hand, anti-VEGF agents act on circulating VEGF, leading to an overall faster treatment response.[29] Therefore, a combined regimen utilizing both pathways might be more effective for ROP treatment than monotherapy, though it could also increases the risk of infection with Anti-VEGF or greater visual field loss or myopia after laser treatment.

Clinicians use the combined treatment for the most complex cases. It is not known whether this treatment is superior to treatment with Anti-VEGF or laser alone and whether there is a lack of response to a sequential treatment of both. When comparing the odds for favorable structural outcomes, the pooled analysis revealed that the combined regimen with laser and anti-VEGF agents was more effective than monotherapy. This combination therapy has several advantages that might include preventing late recurrences of the disease, a study reported late recurrences (as 69 weeks' post-menstrual age) following anti-VEGF agents' monotherapy.[26] Similarly, one of the included studies in our analysis stated that the rate of recurrences was lower in the combination therapy group compared to the monotherapy group.[25] Furthermore, a meta-analysis that compared dense laser and an anti-VEGF agent (intravitreal bevacizumab) found that the rate of retreatment was higher in the anti-VEGF group.[30] This might be explained by the fact that the combination therapy uses the long-term impact of laser ablation in preventing further release of VEGF by ablating the avascular retina. Moreover, one of the included studies in this review reported that the combination therapy was significantly faster in regressing the disease compared to laser monotherapy.[24] Which might be due to the ability of anti-VEGF agents in neutralizing the circulating VEGF molecules.

In all of the included studies in this review, the rate of adverse events was either similar or lower in the combination therapy when compared to monotherapy. Using a combination therapy allows for the usage of less dense laser strategy and an appropriate dose of anti-VEGF agents, which might decrease the adverse events of both modalities.[24–26] A previous study reported more neurodevelopmental impairment when using anti-VEGF agents compared to laser therapy.[31] However, as shown in the included studies in our meta-analysis and another study in the literature, that neurodevelopmental impairment was not observed when using the combination therapy.[32]

One of the limitations of this review is the few numbers of the included studies, and the small number of the participants. Moreover, the risk of bias assessment showed that most of the included studies are of unclear risk bias, which might hinder the quality of evidence of the conclusions of this review. We also did not perform a subgroup analysis based on the classifications of ROP nor the types of anti-VEGF medications due to the limited number of the included studies.

Conclusion

Despite the fact that no statistical significance was found in the pooled analysis, the results show that combination therapy with laser and anti-VEGF agents might be superior to monotherapy, especially in decreasing the rate of ROP recurrence. Combination therapy in the included studies was safe with regards to the perioperative and short-term complications, however, little is known regarding the long-term complications. Future randomized controlled trials are crucial to evaluate the impact of combination therapy with anti-VEGF agents and laser on the long-term structural and functional outcomes in ROP patients, and the associated long-term adverse events. These randomized controlled trials ought to be ideally multicenter studies with adequate number of participants, and preferably with longer follow-up periods.

Abbreviations

ROP, Retinopathy of Prematurity; VEGF, Vascular Endothelial Growth Factor; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, Randomized Controlled Trial; CI, Confidence Interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; DOAJ, Directory of Open Access Journals;

CENTRAL, Cochrane Central Register of Controlled Trials; MeSH, Medical Subject Headings; IVR, Intravitreal Ranibizumab; ETROP, Early Treatment for Retinopathy of Prematurity; OCT, Optical Coherence Tomography; and SE, Spherical Equivalent.

Disclosure

The authors report no conflicts of interest in this work.

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