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Review meta-article

Use of anti-vascular endothelial growth factor (antiVEGF) in the treatment of retinopathy of prematurity (ROP) – A systematic review and a meta-analysis

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Abstract

Introduction: *Retinopathy of prematurity (ROP) is one of the leading causes of blindness in children worldwide. The management of ROP has been revolutionised with the introduction of intravitreal anti-vascular endothelial growth factor (antiVEGF) agents. This review evaluates the safety and efficacy of intravitreal antiVEGF agents when used either as monotherapy, or in combination with laser/cryo in preterm infants with type 1 ROP.*

Methods: *A comprehensive literature search was conducted from 2000 to April 2022 using the following databases PubMed, EMBASE and CINHAL. Total of 12 randomised controlled studies (RCTs) and 7 comparative studies were selected after critical appraisal. RCTs were included in the meta analysis.*

Results: *There were 4628 eyes of 2571 infants with type 1 ROP were identified from the included studies. A meta analysis showed no statistically significant difference in retinal detachment, ROP recurrence, mortality and cerebral palsy between standard treatment (laser/cryo) and antiVEGF mono therapy. AntiVEGF mono therapy may reduce the risk of refractive errors in childhood compared to standard therapy. No significant risk of acute and long-term systemic complications noted with antiVEGF therapy.*

Conclusion: *AntiVEGF agents, as monotherapy is non inferior to standard therapy after evaluating for risk of retinal detachment and recurrence of ROP in infants with type 1 ROP. The data is not sufficient to make strong conclusions favouring routine use anti-VEGF agents as monotherapy in all types of type 1 ROP. Hence, further large scale RCTs with longer follow up period are necessary to evaluate the safety and efficacy of antiVEGF agents for type 1 ROP.*

Background

Retinopathy of prematurity (ROP) is a leading cause of blindness in children in many parts of the world[1-3]. However, the prevalence of ROP changes according to the geographic region. In the industrialized world it is around 5-8%[4]. But in middle income countries ROP prevalence can be very high, sometimes reaching 30%[4]. This high prevalence of ROP in middle income countries is sometimes referred as "third ROP epidemic"[4,5]. The recent improvement of neonatal resuscitation care in middle income countries has improved survival of premature babies[5]. However, most authors believe suboptimal neonatal care may have led to the increase in prevalence of ROP in this region[5].

Retinopathy of prematurity (ROP) was first described in 1942[6]. Till 1950s, relationship between supplementary oxygen and ROP was not known[6]. This finding led to rigid control of oxygen supplementation in the neonatal intensive care units leading to drastic decrease in ROP incidence. However, decrease oxygen supplementation caused an adverse effect on infant morbidity and mortality. With the development of new technology like arterial blood gas analysis, pulse oximetry and other technical improvements in neonatal intensive care services, clinicians have been able to maintain oxygen levels within a reasonable target oxygen saturation level to balance the risk of ROP, morbidity and mortality[6].

ROP is a highly complex disease process initiated by a lack of normal retinal vascularization in preterm

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babies[7]. ROP has a typical progression pattern from stage 1 to 5. But the early disease stages can regress spontaneously at any time. The absence of retinal vessels in the immature retina results in retinal ischemia, leading to the release of multiple growth factors that stimulate vascular growth[7]. When normal vascular development is disturbed by premature birth, new vessels proliferate into the vitreous cavity at the border of the vascular and avascular retina. Vitreous hemorrhage and tractional retinal detachment can occur as the disease progresses[7].

Untreated ROP eventually develops in to a dense, white, fibrovascular plaque behind the lens and complete tractional retinal detachment which was previously called as "retrolental fibroplasia"[7]. Prematurity and low birth weight are the main risk factors of this condition[7]. Other possible risk factors are exposure to varying levels of oxygen concentrations, acidosis, hypercapnia, chronic lung disease, anemia and intraventricular hemorrhage[8].

In 1984, Committee for Classification of ROP, classified ROP according to location (zone to), extent (clock hours 1 to 12), severity (stage 1 to 5) and vascular dilatation/ tortuosity (plus disease)[8,9]. Three zones are centered on the optic disc. Zone lies at the posterior pole and defined as a circle centered at the optic disc with a radius of twice the distance from optic disc to the center of the macula[6]. Zone extend from zone with a radius from optic disc to orra serrata. Zone is defined as the remaining temporal crescent.

Stage 1 ROP is characterized by the presence of a demarcation line which separate the anterior avascular retina from posterior vascular retina. Stage 2 is defined by the presence of an elevated ridge. In this stage, small tufts of new vessels can be seen posterior to the ridge. Stage 3 is characterized by extraretinal fibrovascular proliferation starting at the ridge. Stage 4 has two substages namely stage 4a and stage 4b. Former is defined as partial retinal detachment not involving the fovea. Stage 4b is characterized by partial retinal detachment involving the fovea. When there is total retinal detachment, it is defined as stage 5. Plus, disease is a severe form of ROP characterized by the presence of increasing dilatation and tortuosity of retinal vessels, iris vascular engorgement, pupillary rigidity, and vitreous haze.

In 2006, new definitions were added to include aggressive posterior ROP and pre plus disease[8]. Recently in 2021, third revision of the International classification of ROP has introduced a new terminology for aggressive ROP and it also refined a number of other metrics as well[10].

The Cryo-ROP was the first landmark study in the treatment of ROP and it showed a benefit of cryotherapy in the treatment of threshold disease[11, 12]. In this study, threshold disease was defined as "more than 5 contiguous or 8 cumulative clock hours of stage 3 plus ROP in zone 1 or zone 2"[13]. Threshold disease is considered as a stage with 50% risk of retinal detachment if left untreated[13]. Thus, all eyes with threshold disease were recommended to have cryo treatment. Cryo ROP study was commenced in 1987. Ten-year outcome analysis of Cryo-ROP study revealed that eyes received cryo-therapy were much less likely to develop blindness than control eyes[14].

The Early Treatment for Retinopathy of Prematurity (ET-ROP) study assessed the effect of early treatment for ROP. This early stage was defined as pre-threshold ROP[13]. Later stage was divided in to two groups as type 1 and type 2[13]. Type 1 high risk pre-threshold ROP include "zone 1 plus disease with any stage, zone 1 stage 3 with no plus disease and zone 2 stage 2/3 plus disease". Type 2 low risk pre-threshold ROP include "zone 1 stage 1/2 without plus disease and zone 2 stage 3 without plus disease"[13]. This study randomized infants with bilateral high risk pre-threshold ROP into early retinal ablative treatment and the control eye managed conventionally. Early Treatment for Retinopathy of Prematurity (ET-ROP) study revealed better outcomes after treating early stages of ROP than waiting for threshold disease[15]. ET-ROP study is one of the crucial studies in ROP management as it changed the management of ROP since what we were practicing after Cryo-ROP study. Current management guidelines recommend all eyes with type 1 pre-threshold ROP for early treatment. Type 2 pre threshold ROP is considered as not high risk and follow-up is recommended for such eyes[13].

Vascular endothelial growth factor (VEGF) plays a key role in fetal retinal angiogenesis[6]. In the normally developing retina, VEGF is secreted as a response to the higher oxygen demand of the developing retinal tissue, which results in formation of blood vessels from the optic nerve head to the peripheral retina. Due to high oxygen supplementation in neonatal intensive care units, this response is not optimal, and it is suppressed, leading to suboptimal retinal vascula-

rization. Ultimately this leads to development of significant ischemia in the peripheral retina causing higher secretion of VEGF. Studies have shown very high levels of VEGF in vitreous cavities of infants with partial retinal detachments with ROP[8].

This key role of VEGF in the developing retina has prompted researchers to investigate VEGF inhibition as a potential mode of therapy. The advent of antiVEGF agents has revolutionized the management of many retinal vascular conditions in adults. This also sparked an enthusiasm among researchers to assess efficacy of antiVEGF treatment for ROP.

The first landmark randomized control trial (RCT) to assess antiVEGF for ROP treatment was the BEAT-ROP study (Bevacizumab Eliminates Angiogenic Threat of Retinopathy). In 2011, latter study produced supportive evidence for the use of an antiVEGF as a first line monotherapy for "zone 1 stage 3+ ROP"[16]. There after many studies have tested various anti VEGF agents including pegaptanib, ranibizumab, aflibercept and conbercept for ROP treatment.

The interest with pegaptanib was lost with the development of safer and more effective antiVEGF agents in adults. Bevacizumab is a "recombinant humanized monoclonal antibody"[7]. It blocks angiogenesis by inhibiting vascular endothelial growth factor A[7]. Ranibizumab is developed from Bevacizumab. It is a monoclonal antibody fragment (Fab)[7]. Ranibizumab action is also similar to Bevacizumab. Aflibercept is a recombinant fusion protein. It consist of "extracellular domains of human VEGF receptors 1 and 2 fused to the Fc portion of the human IgG1 immunoglobulin"[7]. Aflibercept binds to circulating VEGF-A, and placental growth factor as well. Some authors believe that it has a superior action than Bevacizumab and Ranibizumab[7]. Conbercept has a similar action to aflibercept and may have more affinity to VEGF than aflibercept[17]. Recent management guidelines recommend treatment of sight threatening ROP or type 1 ROP with laser photocoagulation and or antiVEGF agents[8].

This review has examined all the available evidence of the use of antiVEGF agents in the treatment of ROP. It has assessed the data for safety and efficacy of intravitreal antiVEGF agents when used either as monotherapy, or in combination with laser photocoagulation in preterm infants with type 1 ROP.

Importance of this review

Current management of ROP is mainly with either laser or cryotherapy[8]. Both these treatment modalities cause irreversible damage to the developing retina and most authors believe results are far from perfect. Thus, there is a need for a new effective treatment modality which is less destructive than the current therapy. AntiVEGF treatment for ROP brought hope for a new less destructive treatment option.

However, still there are many unaddressed areas in relation to the use of antiVEGF treatment for ROP [8]. Authors of BEAT-ROP study have concluded that their study is not powered enough to assess the safety of bevacizumab treatment for ROP[16]. Furthermore, significant number of studies published up to date have failed to document the recurrence of ROP with antiVEGF monotherapy[4]. A recent systematic review has also concluded that there is insufficient evidence to decide on effective and safe therapy for ROP [4].

After BEAT ROP trial, there are many studies published on treatment for ROP with newer antiVEGF agents like ranibizumab, aflibercept and conbercept. There is paucity of systematic reviews which contain analysis of treatment of ROP with all available antiVEGF agents at the present time.

This review has examined the available high-quality evidence for the use of anti VEGF drugs including all currently available agents (bevacizumab, ranibizumab, aflibercept and conbercept) for the treatment of ROP. A meta analysis was undertaken of all available randomized control trials up to date

Objective

To assess the safety and efficacy of intravitreal antiVEGF agents when used either as monotherapy, or in combination with laser photocoagulation in preterm infants with type 1 ROP.

This review has compared the currently available evidence for the efficacy of antiVEGF monotherapy with laser / cryo therapy. It has also investigated the efficacy of combination therapies of laser and antiVEGF treatment. In addition to clinical outcome, data has collected and analyzed on dosage, frequency of injections, complications, and safety.

Methods

This review adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance and the guidelines in the Cochrane Handbook to conduct the study[18].

Inclusion criteria

This systematic review has collected data from randomised, quasi randomised controlled studies, and high-quality comparative studies published during the last 22 years (from year 2000 to April 2022) which evaluated the efficacy and safety of antiVEGF (Bevacizumab, Ranibizumab, Aflibercept, Conbercept) monotherapy or combinations of therapy with laser / cryo therapy for preterm babies with type ROP.

The study population was defined as "preterm infants born before 37th week of gestational age with type 1 ROP". Latter is defined as "ROP in zone I with any stage with plus disease, zone I with stage 3 ROP with or without plus disease, or zone II with stage 2 or 3 ROP with plus disease"[10].

Exclusion criteria

Studies that contain pegaptanib, ROP other than type 1 ROP, and patients with significant other co-existing systemic pathologies at diagnosis were excluded from this review.

Interventions

Objective 1

Intervention – intravitreal antiVEGF
Control – Laser / cryo therapy (standard treatment)

Objective 2

Intervation – intravitreal antiVEGF B
Control – intravitreal antiVEGF A

Objective 3

Intervention – combination treatment (antiVEGF +LASER treatment)
Control – Laser / cryo therapy (standard treatment)

Outcome measures

Primary outcome

An adverse outcome with progression to a retinal detachment involving the macula or visual loss (acuity <20 / 200) or blindness.

Secondary outcomes,

I. Unfavorable functional outcomes (amblyopia, nystagmus, refractive error in either eye) at 6 to 12 months of corrected age.

II. Unfavorable structural outcomes (retinal fold involving the macula, retrolental tissue or 'mass' obscuring the view of the posterior pole) at 6 months to 12 months of corrected age.

III. Mortality (death before discharge from the primary hospital or death before two years corrected age).

IV. Recurrence of ROP requiring retreatment up to 6 months of age.

V. Local adverse effects (conjunctival haemorrhage, vitreous haemorrhage, and endophthalmitis after intravitreal injection).

VI. Acute systemic effects (apnea requiring respiratory support and cardiorespiratory arrest during or immediately after the treatment).

VII. Delayed systemic effects (cerebrovascular accidents / myocardial dysfunction based on ECG parameters diagnosed in the first 24 months of life).

VIII. Adverse neurodevelopmental outcomes at 18 months to 24 months of corrected age (cerebral palsy, moderate to severe developmental delay.

Literature search

A comprehensive literature search conducted in major electronic databases including PubMed, Embase and CINHAL from year 2000 to April 2022. We used the following search terms, antiVEGF OR anti vascular endothelial growth factor AND retinopathy of prematurity OR ROP.

There were no language restrictions applied for the literature search. We limited our search to human studies. We also manually searched clinical trial registries (clinicaltrials.gov and ISRCTN registry) for ongoing and recently completed trials.

Unpublished data was hand searched in the major conference proceedings (American Academy of Ophthalmology annual meeting and World Ophthalmology Congress). In addition, reference lists of selected landmark studies were thoroughly investigated for relevant literature.

Non comparative or nonrelevant comparison studies, editorials, conference abstracts, review articles, letters to the editor, case reports, duplicate reports, non-relevant topic, and animal experimental studies were excluded.

Data collection

Two independent reviewers screened the titles and abstracts to identify potentially relevant studies. If necessary full text articles were reviewed if the reviewers could not decide the relevance by screening title and abstract. Screened studies were subjected to full text retrieval. For non-English language articles, every attempt was made to find the English translations.

Data was extracted using a preformed pilot tested data extraction sheet designed according to the inclusion/ exclusion criteria. Any disparity between the two authors were resolved by discussion. We contacted relevant study investigators for additional information (e.g., clarify methods of randomization, definition of events, study participant characteristics etc.)

Assessment of risk of bias

Two authors independently assessed the risk of bias in all included studies. ROB-2 tool was used to assess bias in the randomised control studies[19]. ROBINS-I tool was used to assess risk of bias in non-randomised controlled studies[20]. All disagreements were resolved by discussion or by a third assessor.

Assessment of heterogeneity

We assessed heterogeneity by calculating Chi-square test with significance set at P value less than 0.05, and by calculating I^2 value. Meta analysis with I^2 less than 30% considered as low heterogeneity and more than 70% considered as high heterogeneity.

We used a random effect model for this meta analysis when there is significant heterogeneity between studies. Otherwise, a fixed effect model was used. In addition, we drew forest plots to show variation and to explore heterogeneity

Subgroup analysis / investigation of heterogeneity

We analysed following subgroups for more refined calculations and to reduce heterogeneity.

I. According to specific antiVEGF agent used (bevacizumab / ranibizumab / aflibercept/ conbercept)

II. According to location of ROP at enrolment (zone 1 or 2)

III. According to type of ablation (laser or cryo)

Level and quality of evidence assessment

All selected studies were graded according to the level of evidence formulated by the Scottish intercollegiate guidelines network[21]. Quality of evidence of the studies were assessed by two independent authors according to the GRADE approach as outlined in GRADE handbook[22]. Any disagreement was resolved by discussion.

Dealing with missing data

Data which was measured but not reported were requested from the relevant study authors. When there was a discrepancy between number randomised and number treated, we reported missing data as lost to follow up.

Data synthesis

We used Review Manager 5.4 to analyze of all quantitative data[23]. Mantel-Haenszel statistical method was used for all dichotomous outcomes to calculate odds ratio as the effect measure. For continuous variables, inverse variance statistical method was used to calculate mean difference as the effect measure.

Results

Search results

From data base and registry search we identified 844 records. Out of these 62 duplicates were removed. In addition, 18 records were also removed which we could not find English language translations. Further 608 articles were removed after title and abstract screening leaving 156 records for full text retrieval. In addition, by manual search we identified 23 articles for full text retrieval. Out of these, 19 studies were selected for data analysis. This includes 12 randomised control studies and 7 comparative studies. Please refer chart 1 for PRISMA diagram.

Description of all included studies

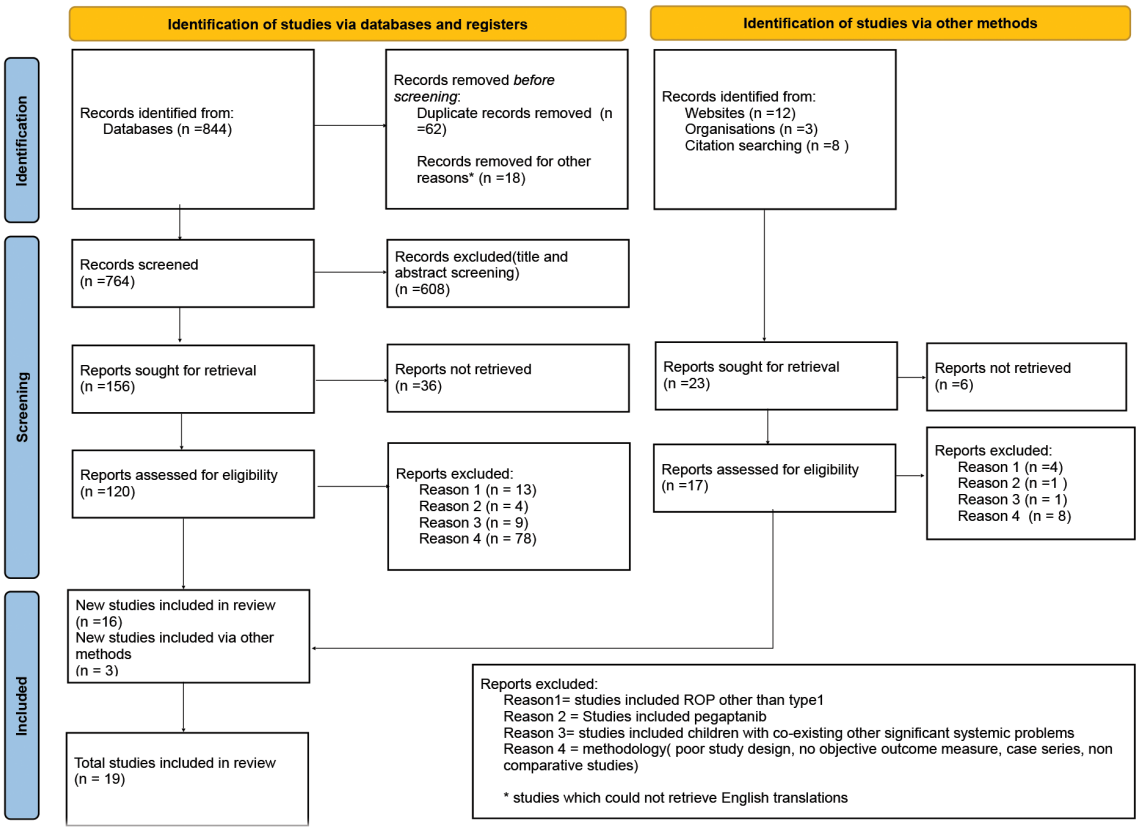
Please see table 1 for brief description of all included studies.

Table 1.

Study	Type	Level of evidence	Sample size	Intervention	Main out comes	Results
Mintz-Hittner 2011	RCT/Randomised control trial	1++	300 E 150 I	IVB/Intravitreal Bevacizumab(0.625mg) vs laser	Recurrence as of ROP in one or both eyes requiring retreatment	IVB as compared with laser therapy, in infants with stage 3+ ROP showed a significant benefit for zone I but not zone II disease
Geloneck 2017	RCT	1+	255 E 131 I	IVB(0.625mg) vs laser	Refractive outcomes	Very high myopia in eyes that received laser treatment than in eyes that received IVB
Isaac 2015	Comparative	2++	45 E 25 I	IVB (0.625) vs laser	compare structural outcomes & visual function for infants with type 1 ROP	Both showed good structural outcome, and no difference in visual acuity or refraction
Erol 2015	comparative	2+	36 E 20 I	IVR (0.25 mg) vs IVB (0.625 mg)	ROP recurrence	The incidence recurrence was higher in eyes which received IVR
Karkhaneh 2016	RCT	1+	158 E 80 I	IVB(0.625mg) vs laser	ROP persistence or recurrence	Recurrence of neovascularization with IVB monotherapy seems to be higher than that laser therapy
O'keeffe 2016	RCT	1+	30 E 15 I	IVB(1.25mg) vs LASER	ROP regression, recurrence	IVB treated eyes showed rapid regression of the ROP with resolution of the plus disease
Wallace 2017	RCT	1-	122 E 61 I	IVB at 0.25 mg, 0.125 mg, 0.063 mg, and 0.031 mg	To find a dose of IVB that was lower than previously used for severe ROP	A dose of IVB as low as 0.031 mg was effective in 9 of 9 eyes in this phase 1 study and warrants further investigation.
Zhang 2017	RCT	1+	100 E 50 I	IVR/Intravitreal Ranibizumab(0.30mg) vs LASER	ROP recurrence	substantial risk of recurrence of ROP after a single-dose IVR
Mueller 2017	Comparative	2+	108 E 54 I	IVB (0.625) vs laser	ROP regression and recurrence	IVB leads to faster regression of active ROP in infants with posterior ROP compared with laser photocoagulation
Wallace 2018	RCT	1-	122 E 61 I	IVB at 0.25 mg, 0.125 mg, 0.063 mg, and 0.031 mg	Late recurrence and complications	Re-treatment for failure or late recurrence was not associated with initial dose or category of type 1 ROP at baseline
Kennedy 2018	RCT	1+	32 E 16 I	IVB (0.625) vs laser	assess the effects of IVB on non-ophthalmologic outcomes	IVB versus laser therapy for retinopathy of prematurity showed no adverse effects on medical or neurodevelopmental outcomes.
Stahl 2018	RCT	1-	19 E 19 I	IVR 0.12 mg vs 0.20 mg	Need for rescue therapy	Both IVR doses were equally successful in controlling acute ROP
Kang 2018	Comparative	2+	153 E 83 I	IVB (0.625 mg) vs IVR (0.2 mg)	ROP recurrence	Both IVB and IVR achieved a low rate of complications and recurrence
Stahl 2019	RCT	1+	225 E 225 I	IVR 0.2mg vs 0.1mg vs laser	survival with no active ROP, unfavourable structural outcomes, or the need for an additional treatment	treatment of ROP with IVR 0.20mg might be superior to laser therapy
Natarajan 2019	Comparative	2+	405 E 405 I	IVB (0.625) vs laser/Cryo	death or severe neurodevelopmental impairment (NDI)	ROP treatment modality was not associated with differences in death or NDI, but the IVB group had higher mortality and poor cognitive outcomes in early childhood
Cheng 2020	Comparative	2+	1199 E 625 I	IVC/Intravitreal Conbercept 0.25mg vs IVR 0.25 mg	Regression, progression, or recurrence of ROP	IVC and IVR are effective for treating ROP. Compared with IVR, IVC resulted in less recurrence and longer treatment intervals.
Stahl 2021	RCT	1+	32 E 16 I	IVR 0.2mg vs 0.1mg vs laser	Neurodevelopmental and functional ocular outcomes	Neurodevelopmental and functional ocular outcomes at 1 and 2 years after treatment with IVR are reassuring regarding long-term safety
Barry 2021	Comparative	2+	1167 E 640 I	antiVEGF vs laser	Retinal Detachment after Treatment of with Laser versus antiVEGF	antiVEGF therapy results in better short-term structural outcomes than laser therapy when type 1 ROP is treated before 36 weeks' PMA
Wu 2021	RCT	1+	120 E 60 I	IVC 0.25mg vs IVR 0.25 mg	ROP recurrence	Both IVC and IVR are effective therapies for the treatment of ROP.

(E - eyes, I - infants, IVB - intravitreal bevacizumab, IVR - intravitreal ranibizumab)

Chart 1. PRISMA flowdiagram.



Description of included studies in the meta-analysis

Mintz-Hittner 2011[16] – (BEAT-ROP Study)

This is a randomised controlled, prospective, stratified, multicentre trial to assess IVB monotherapy for "zone I or zone II posterior stage 3+ retinopathy of prematurity". Study participants were randomly assigned to receive IVB ("0.625 mg in 0.025 ml of solution") or conventional laser therapy, bilaterally. Study showed IVB monotherapy in infants with stage 3+ retinopathy of prematurity has a "significant benefit for zone I but not for zone II disease". Study also stated that peripheral retinal vessels continue to develop after treatment with IVB. Laser treatment arrest peripheral vascular development with the cost of permanent destruction of the peripheral retina. This trial was not powered enough to assess safety.

Geloneck 2017[24]

This is a follow up study of infants treated in BEAT ROP study[16]. Aim of this study was to report refractive outcomes in preterm infants with "ROP in zone I or zone II posterior with stage 3+ ROP or aggressive posterior ROP (APROP)". Study revealed high incidence of myopia in eyes that treated with laser treatment than in eyes that had intravitreal bevacizumab. Significant number of study participants (18%) were lost to follow up during the study. This study also has a potential source of observer bias since the lead investigator himself performed refraction.

Karkhaneh 2016[25]

This study is a randomised controlled non-masked prospective clinical trial conducted to assess the effect of IVB for "Type 1 retinopathy of prematurity in zone II". Study revealed higher recurrence of neovascularization with IVB monotherapy compared to standard laser treatment among infants with "Type 1 ROP in zone II". However, study also showed reinjection of IVB causes regression in significant number of recurrent cases. Furthermore, this study also revealed a statistically significant lower birthweight in infants who had treatment failure.

O'Keeffe 2016[26]

This is a randomized controlled prospective study conducted to compare IVB with diode laser in preterm

infants with "Zone 1 posterior and Zone 2 ROP". Study analysed regression of ROP, complications of treatment, refraction, and other systemic complications. Study revealed rapid regression of ROP in the IVB group with the resolution of the plus disease. It also showed flattening of the ridge at 48 hours in the IVB group. But complete regression took more than twelve weeks. Neuroimaging showed no adverse effects which can be attributed to IVB. Significant myopic shift noted in eyes treated with Laser. VEP showed no difference between the two groups. Study also reported no systemic adverse effects associated with IVB. Only 15 infants were incorporated for the study.

Wallace 2017[27]

This masked, multicentre, phase 1 dose de-escalation study was conducted to assess the IVB dose which is lower than the previously used standard dose for severe ROP. Infants with type 1 ROP in 1 or both eyes were enrolled. Study concluded IVB dose as low as 0.031 mg is effective for type 1 ROP. Study authors also stressed the need of large scale studies to confirm their finding.

Zhang 2017[28]

This prospective, randomised controlled, single centre trial compared IVR monotherapy with laser treatment for ROP in Zone II. Total 100 eyes incorporated for the study. It revealed that IVR treatment continue to promote the vascularization of peripheral retina with regression of ROP. However, a considerable number of infants developed recurrence of ROP after a single-dose IVR. Study didn't recommend IVR as a single-dose monotherapy for Zone II ROP. This study is restricted only to a single ethnic group.

Wallace 2018[29]

Follow up study of initial "masked, multicentre, dose de-escalation study" (Wallace 2017). This study examined the need of additional treatments, early and late ROP recurrences, and structural outcomes after 6 months. Study concluded that structural outcomes after low dose IVB therapy is comparable to standard dose. It also showed that many eyes needed additional treatment after low dose IVB treatment.

Kennedy 2018[30]

The purpose of this multicentre randomized trial was to assess the non-ophthalmologic outcomes after IVB treatment on infants with stage 3+ ROP (zone I or zone II posterior in both eyes). Total 18 infants recruited for the study. Study revealed no significant differences between the IVB group and laser group in terms of length, weight, head circumference, cerebral palsy, and Bayley scores. However, bevacizumab group showed statistically significant reduction in duration of hospital stay compared to laser group. Study concluded that IVB has no adverse effects on medical or neurodevelopmental outcomes.

Stahl 2018[31] – CARE-ROP study

This randomised multicentre, double blind, investigator initiated study was conducted to investigate the efficacy of lower doses of ranibizumab (0.12 mg vs 0.20 mg) treatment for infants with "bilateral aggressive posterior ROP, ROP stage 1 with plus disease, stage 2 with plus disease, or stage 3 with or without plus disease in zone I or ROP stage 3 with plus disease in posterior zone II". Nineteen infants were randomised in the study. It concluded that 0.12 mg IVR (24% of the standard adult dose) is equally effective as 0.20mg IVR (40% of the adult standard dose). Study also demonstrated that 0.12mg IVR leads to superior vascularization of the peripheral retina

Stahl 2019[32] – RAINBOW study

This is a randomised, multicentre, 3-arm, parallel-group study. The study compared the safety and efficacy of intravitreal injection of ranibizumab 0.2mg, ranibizumab 0.1mg and laser therapy. Study revealed that 0.1mg IVR has no advantage over 0.2mg IVR. Authors found that IVR 0.2mg has an acceptable safety profile and concluded that it was more effective than laser treatment with fewer ocular adverse outcomes. This study was industry sponsored and all parties had access to the outcome data. Study authors have received funding before and during the study from the industry. Statistical analysis was done by third independent author.

Stahl 2021[33]

This is a follow up study of CARE ROP trial. This study assessed the long-term functional outcomes, neurodevelopment outcomes and safety. Study concluded that there is no statistically difference between 0.12mg and 0.20 mg IVR therapy in terms of neuro development and functional outcomes at 1 and 2 years. However, study also stated that ranibizumab therapy need regular follow up as there is a risk of reactivation of ROP.

Wu 2021[34]

This multicentre, randomised controlled, prospective trial compared safety and efficacy of intravitreal conbercept (IVC) and IVR for the treatment of type 1

ROP. Total number of 60 infants were incorporated in the study. Study assessed the recurrence and complications of treatment during follow up of 6 months. Study concluded that there is no statistically significant difference between the two treatment groups, and both are safe and effective. Small number of study participants and shorter period of follow up are major limitation of the study.

Risk of bias in included randomised controlled studies

Please refer to chart 2 for risk of bias summary of the included randomised controlled studies in this review.

Chart 3 shows the risk of bias graph of all included randomised controlled studies.

Chart 2.

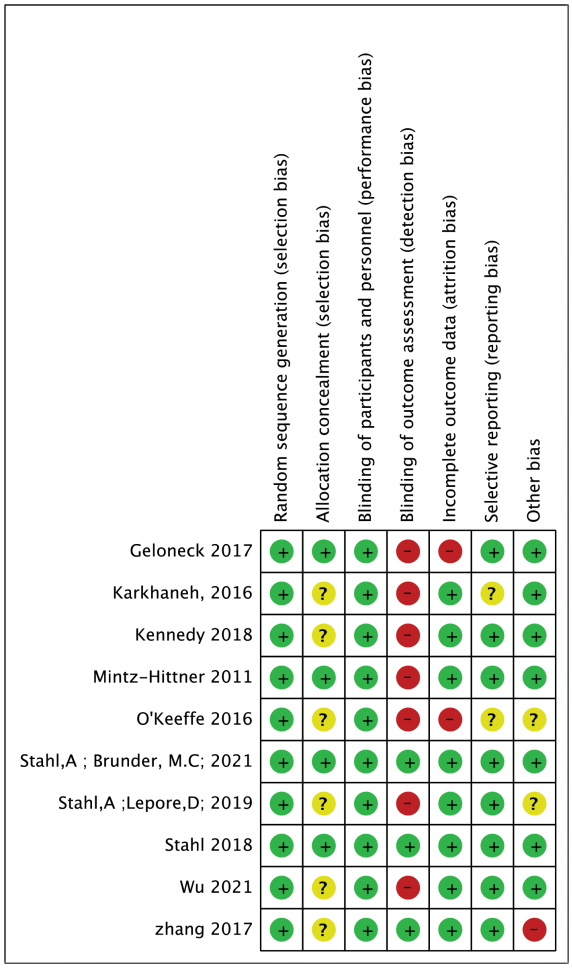
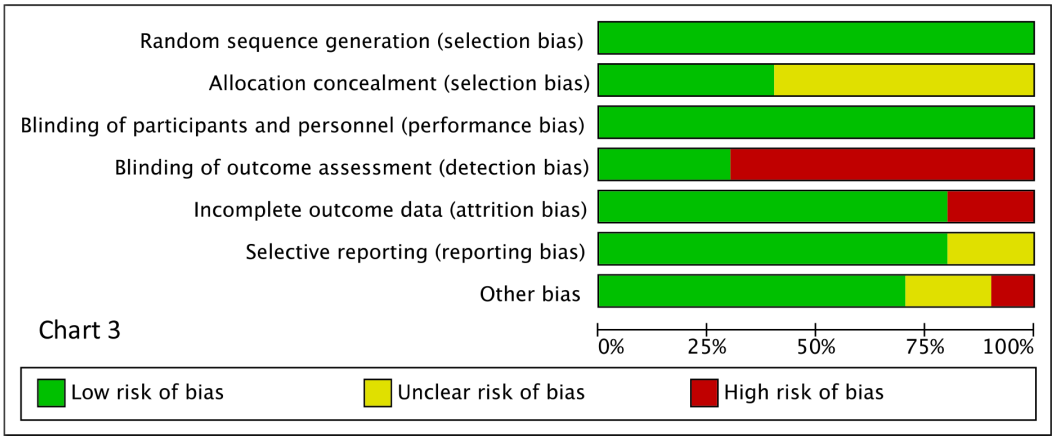


Chart 3.



All the RCTs in this review have good randomisation sequence. Four RCTs have good allocation concealment (Geloneck 2017, Mintz-Hittner 2021, Stahl 2021, Stahl 2018)[16,24,31,32]. The remaining RCTs did not provide enough details to decide on satisfactory allocation concealment. None of the authors replied to our request regarding details on allocation of study subjects up to the date of submission of the report.

Masking of study participants is not feasible due to the nature of intervention. However, as the study participants are very young, it is unlikely that masking of study participants have an impact on outcomes. Impact of the masking of caregivers on outcomes are unknown. None of the included studied have masked care givers. Masking of outcome assessment was done only in three studies (Stahl 2021, Stahl 2018, Zang 2017)[27, 31, 32].

Only two studies showed high risk of attrition bias (O'Keefe 2016, Geloneck 2017)[26]. Latter studies have relatively high lost to follow up rate. Unclear risk of selective reporting was shown in two studies (Karkhaneh 2016, O'Keefe 2016) as they failed to give clear subgroup analysis[25,26].

Zhang 2017 study was completely restricted to single ethnicity which is a potential source of bias[28]. O'Keefe 2016 has randomised two eyes of the infant for intravitreal injections and laser[26]. Because of the systemic absorption antiVEGF agent, the control eye which had laser may show better outcome as it has the potential risk of exposure to systemically absorbed antiVEGF. Stahl 2019 study has been completely funded by a major pharmaceutical company. Even though the study authors have mentioned that they are independent, the pharma company had the full access to data, and they owned it. Hence there is a potential source of unclear bias.

Description of excluded studies from Meta analysis

Isaac 2015 [35]

Retrospective study done in Toronto, Canada in 2013. This comparative study assessed structural outcomes, vision, refraction, and frequency of follow-up for infants with type 1 ROP in zone I or zone II posterior treated with IVB versus laser. Total of 25 study participants were recruited. This study concludes both treatment modalities have resulted in good structural outcomes, and no difference in visual acuity or refraction. More frequent follow-ups seen in the IVB group. Failure of masking of outcome assessment, small number of study participants and shorter period of follow up (9 months) are major limitations of this study.

Mueller 2017[36]

Retrospective study which investigated the outcomes of intravitreal bevacizumab compared with laser photocoagulation in type 1 retinopathy of prematurity. This study was conducted in Berlin, Germany. Total 54 study participants (IVB 37, Laser 17). Study concluded that IVB causes relatively faster regression of active ROP in infants with posterior ROP compared with laser treatment. Study also stated that there is no difference in the spherical equivalent after 12 months in those treated with IVB and laser photocoagulation. However, subgroup analysis revealed more myopic refraction in posterior ROP than in peripheral zone II.

Barry 2021[37]

Nonrandomised comparative cohort study which compared the rates of short-term retinal detachment in infants treated for type 1 retinopathy of prematurity with intravitreal anti vascular endothelial growth factor treatment and laser treatment. This study included 640 infants (1167 eyes). Care givers or examiners were not masked. This study revealed anti vascular endothelial growth factor treatment gives better short-term structural outcomes than laser treatment when type 1 ROP is treated before 36 weeks' post menstrual age. In addition, study also concluded that after 36 weeks of post menstrual age, both treatment modalities have very low rates of RD.

Natarajan 2019[38]

Retrospective comparative study. Study compared IVB treatment with laser therapy for adverse outcomes in early childhood. Study included 405 infants. Masking was not done. This study concluded ROP treatment method was not associated with differences in death or neuro developmental outcomes. However, subgroup analysis revealed the bevacizumab group had higher mortality and poor cognitive outcomes in early childhood.

Cheng 2020[39]

Retrospective comparative study. Main purpose of the study was to compare effectiveness of conbercept with ranibizumab for type 1 retinopathy of prematurity. Total of 145 infants were included in the study. Masking of caregivers or outcome assessment were not done. This study concluded that conbercept is non inferior to ranibizumab in treating for retinopathy of prematurity. In addition, study also revealed compared

to ranibizumab, conbercept gives less recurrence and longer treatment intervals.

Erol 2015 [40]

Retrospective study. It compared the efficacy of intravitreal ranibizumab therapy with bevacizumab therapy for type 1 retinopathy of prematurity. Total of 422 study participants included in the study. Masking of outcome assessment has not been done. Study revealed higher incidence of recurrence in the ranibizumab group.

Kang 2018 [41]

Retrospective comparative study. This study investigated the efficacy, safety, and anatomical outcomes associated with Ranibizumab and Bevacizumab therapy for retinopathy of prematurity. Total of 100 infants were included in the study. Outcome assessment was not masked. Study concluded no significant difference in recurrence, retinal vascularisation, complications, and spherical equivalent.

Outcome analysis

Primary outcome: An adverse outcome with progression to a retinal detachment involving the macula or visual loss (acuity <20/200) or blindness.

Six RCT's have assessed progression to retinal detachment within six months to 1 year after commencement of the treatment. Though the meta analysis favours laser treatment, there was no statistically significant difference between standard treatment and antiVEGF treatment (OR: 1.96, 95%CI: 0.74-5.23, I^2: 0%, Figure 1). There were not enough data for subgroup analysis (e.g., effect of combination therapy, effect of individual antiVEGF).

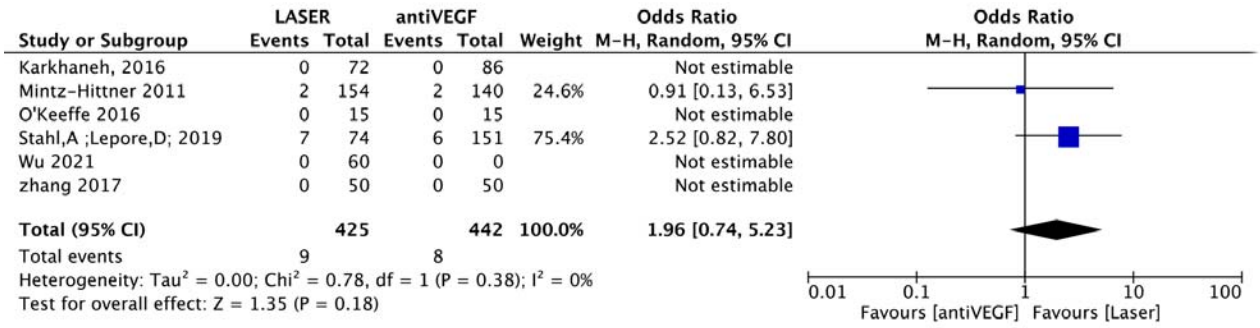


Figure 1.

Figure 2 shows quality of evidence for the above Meta analysis.

Summary of findings:

Retinal detachment comparison antiVEGF vs LASER/CRYO for Type 1 ROP

Patient or population: Type 1 ROP
Setting: Neonatal units
Intervention: antiVEGF
Comparison: LASER/CRYO

Outcomes	Anticipated absolute effects* (95% CI) Risk with LASER/CRYO	Risk with antiVEGF	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
New Outcome	18 per 1,000	**35 per 1,000** (13 to 88)	**OR 1.96** (0.74 to 5.23)	867 (6 RCTs)	⨁⨁⨁◯ Moderate[a]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. outcome assessment not masked

Figure 2.

One non randomised cohort study (Barry 2021) showed antiVEGF therapy results in better short term retinal detachment rate than laser therapy when type 1 ROP is treated before 36 weeks' post menstrual age. After this age, both treatments have very low rates of RD[37].

None of the included studies which compared ranibizumab vs conbercept have data for retinal detachment rates[34, 39].

Secondary outcomes

1. Recurrence of ROP

Five RCT's reported recurrence of ROP with antiVEGF vs laser / cryo. Figure 3 shows Meta analysis and Forest plot for the latter studies. This analysis slightly favours standard treatment. But there is no statistically significant difference between the two groups (OR: 2.59, 95%CI: 0.44-15.36). However, the heterogeneity of the analysed data was very high (I^2 - 90%).

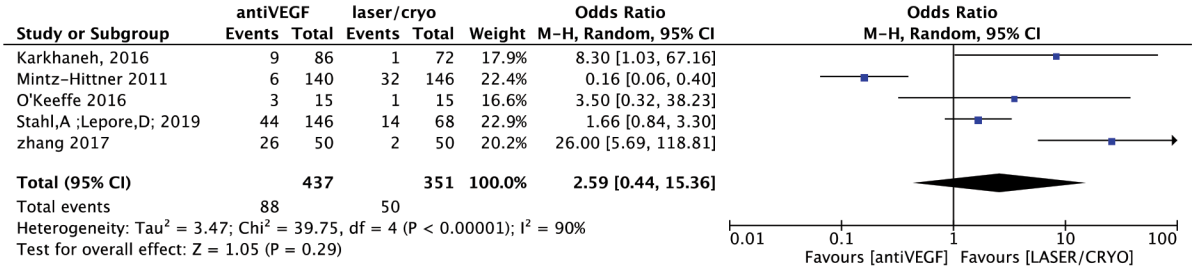


Figure 3.

Figure 4 shows the quality of evidence analysis for the latter set of studies. It shows certainty of evidence is low.

Summary of findings:

Recurrence of ROP antiVEGF compared to LASER/CRYO for Type 1 ROP

Patient or population: Type 1 ROP
Setting: Neonatal units
Intervention: recurrence of ROP antiVEGF
Comparison: LASER/CRYO

Outcomes	Anticipated absolute effects* (95% CI) Risk with LASER/CRYO	Risk with recurrence of ROP antiVEGF	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
recurrenece of ROP	142 per 1,000	**301 per 1,000** (68 to 718)	**OR 2.59** (0.44 to 15.36)	788 (5 RCTs)	⨁⨁◯◯ Low[a,b]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Outcome assessment not masked
b. high heterogeneity

Figure 4.

Figure 5 shows Forrest plot which compared Intravitreal Bevacizumab (IVB) and standard therapy. This subgroup analysis showed no statistically significant difference between the two interventions (OR: 0.84, 95%CI: 0.08-8.91, I2 : 74%). As in the previous analysis, heterogeneity in this analysis was also high.

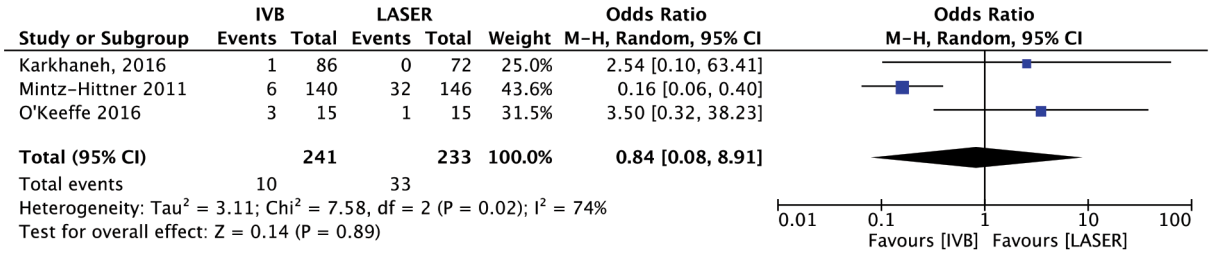


Figure 5.

Figure 6 provide the quality of evidence for the latter analysis. It shows moderate certainty of evidence.

Summary of findings:

Recurrence of ROP- IVB compared to LASER/CRYO

Patient or population: Type 1 ROP
Setting: Neonatal units
Intervention: IVB
Comparison: LASER/CRYO

Outcomes	Anticipated absolute effects* (95% CI) Risk with LASER/CRYO	Risk with IVB	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Recurrence of ROP - IVB VS LASER	142 per 1,000	**122 per 1,000** (13 to 595)	**OR 0.84** (0.08 to 8.91)	474 (3 RCTs)	⨁⨁⨁◯ Moderate[a,b]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. outcome assessment not masked
b. high heterogeneity

Figure 6.

One comparative study (Erol 2015) analysed recurrence of ROP between IVB vs intravitreal ranibizumab (IVR) and revealed higher recurrence with IVR[40].

Further subgroup analysis was done to compare recurrence of ROP after IVR 0.1mg vs 0.2mg. This subgroup analysis included two studies, Stahl 2019[32] and Stahl 2018[42]. It revealed no statistical difference between the two groups (OR: 0.04, 95%CI: -0.05-0.12, I^2 : 0%). Figure 7 shows the meta analysis and Forrest plot for the latter comparison and Figure 8 gives the quality of evidence.

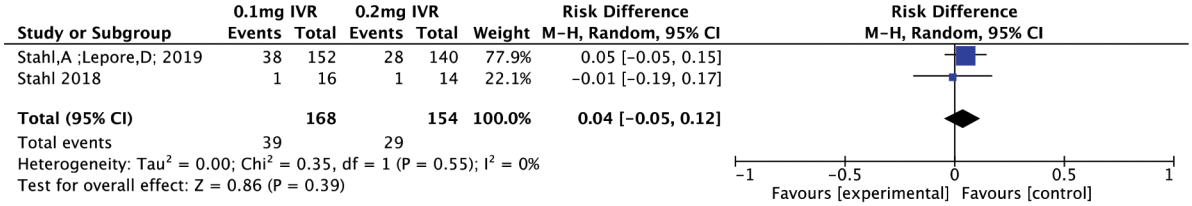


Figure 7.

Summary of findings:

IVR 0.1mg compared to IVR 0.2mg for Type 1 ROP

Patient or population: Type 1 ROP
Setting: neonatal units
Intervention: IVR 0.1mg
Comparison: IVR 0.2mg

Outcomes	Anticipated absolute effects* (95% CI) Risk with IVR 0.2mg	Risk with IVR 0.1mg	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Recurrence of ROP with lower dose aganist standard dose	188 per 1,000	**233 per 1,000** (150 to 344)	**OR 1.31** (0.76 to 2.26)	322 (2 RCTs)	⨁⨁⨁◯ Moderate[a]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. outcome assessment not masked

Figure 8.

Wu et al. in his 2021 RCT which compared ranibizumab vs conbercept showed no statistical significance between recurrence of ROP and time to recurrence between the two groups[34]. One retrospective study (Cheng 2020) showed less recurrence and longer time to recurrence with conbercept compared to ranibizumab[39].

2. Neuro developmental outcomes

Figure 9 shows a meta analysis from two studies which reported cerebral palsy during their follow up. It showed no statistically significant difference between the two groups (OR: 1.40, 95%CI: 0.14-13.57).

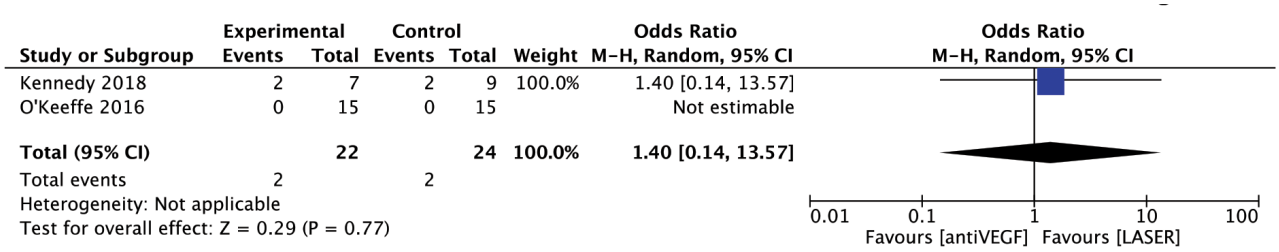


Figure 9.

However, certainty of evidence is very low (Figure 10). Different studies have reported neuro-developmental outcomes with different parameters. Thus, there were only few studies suitable to include in the analysis.

One retrospective multicentre cohort study (Natarajan 2019) concluded that neuro development impairment in early childhood was not significantly different among extremely preterm infants treated with laser or IVB[38]. None of the included studies have compared conbercept with LASER / IVB for neuro developmental outcomes.

Summary of findings:

Neuro-developmental outcomes antiVEGF compared to LASER/CRYO

Patient or population: Type 1 ROP
Setting: Neonatal units
Intervention: antiVEGF
Comparison: LASER/CRYO

Outcomes	Anticipated absolute effects* (95% CI) Risk with LASER/CRYO	Risk with antiVEGF	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Cerebral palsy-antiVEGF vs LASER	83 per 1,000	**113 per 1,000** (13 to 552)	**OR 1.40** (0.14 to 13.57)	46 (2 RCTs)	⨁◯◯◯ Very low[a,b,c]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. outcome assessment not masked
b. different length of follow up periods
c. number of events too small

Figure 10.

3. Mortality

Four randomised controlled studies (Mintz-Hittner 2011, Karkhaneh 2016, O'Keeffe 2016, Kennedy 2018) have reported mortality during their follow up[16, 25, 26, 30]. Figure 11 shows the meta analysis for mortality which compare standard treatment against Intravitreal Bevacizumab, and it shows no statistical significance between the two groups (OR: 2.81, 95%CI: 0.54-14.75).

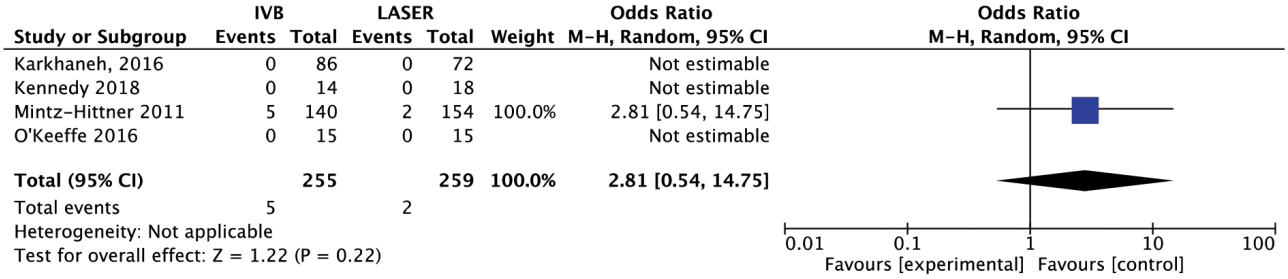


Figure 11.

Figure 12 shows the quality of evidence for the above Meta analysis. Because of small number of events, variable follow up and lack of blinding the quality of evidence is low.

Natarajan et al. in his comparative study concluded that mortality in early childhood was not significantly different among extremely preterm infants treated with laser surgery or bevacizumab[38]. None of the included studies have compared conbercept with LASER / IVB for mortality in early childhood.

Summary of findings:

Mortality in AntiVEGF compared to LASER/CRYO in the treatment of type 1 ROP

Patient or population: Type 1 ROP
Setting: neonatal units
Intervention: AntiVEGF
Comparison: LASER/CRYO

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with LASER/CRYO	**Risk with AntiVEGF**				
Mortality-IVB vs LASER	8 per 1,000	**21 per 1,000** (4 to 103)	**OR 2.81** (0.54 to 14.75)	514 (4 RCTs)	⨁◯◯◯ Very low[a,b,c]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. outcome assessment not masked
b. variable follow up periods
c. small number of events

Figure 12.

4. Refractive outcomes

One RCT, Geloneck 2014[24], and two comparative studies, Mueller 2017 and Isaac 2015[35,36], have reported refractive outcomes with adequate data.

Geloneck et al. reported more very high myopia with eyes received laser treatment than in eyes that received intravitreal bevacizumab[24]. Another RCT, O'Keeffe et al. has reported significantly higher occurrence of myopia in laser treated group. But latter study has not reported outcome data[26].

Mueller et al. conclude that after 12 months, spherical equivalent was not statistically significant difference between IVB and laser photocoagulation in posterior ROP patients[36]. However, the same study also reported intravitreal bevacizumab lead to a significant lower spherical equivalent in infants with posterior ROP (+0.37 dioptre) compared with peripheral zone II ROP (+3.0).

Contrary to latter two studies, Isaac et al. concluded no difference in visual acuity or refraction with intravitreal bevacizumab vs laser after 1 year follow up[35].

None of the included studies have compared conbercept with laser / IVB for refractive outcomes.

5. Local adverse effects

Two studies (Zhang 2017 and Karkhaneh 2016) have reported no cases of endophthalmitis, cataract and vitreous haemorrhage in their study population[25, 28]. Mintz-Hittner et. al has reported no significant difference in the incidence of cataract removal between IVB and laser treated groups[16].

None of the other included studies have reported figures on sub conjunctival haemorrhage, endophthalmitis, vitreous haemorrhage and cataract after interventions.

6. Acute and delayed systemic effects

Kennedy et al. followed up the BEAT ROP study participants for 2 years to assess the non-ophthalmological outcomes[30]. This study has showed no adverse effects on medical or neurodevelopmental outcomes with bevacizumab compared to laser therapy[30].

One study (Stahl 2018) which compared ranibizumab 0.12mg vs 0.20mg revealed no difference in ocular and non ocular adverse effects between the two groups[42]. More importantly, the same study showed no difference in the systemic ranibizumab levels in the two groups highlighting limited systemic absorption of ranibizumab.

None of the other included studies have compared acute / delayed systemic effects between laser and antiVEGF.

Discussion

Summary of main findings

This systematic review identified 12 randomised controlled trials (RCTs) and 7 comparative studies. Meta-analyses were performed only including data from RCTs. Four comparative studies and five RCTs have compared IVB vs laser/cryo. One comparative study has compared IVR and IVB. There were two studies (One comparative study and one RCT) which compared IVR and IVC. Two RCTs have compared lower doses of IVB and another RCT has compared lower doses of IVR. This review did not identify studies which compare combination of treatment (laser+ antiVEGF) with standard treatment (laser / CRYO).

This meta-analysis showed no statistically significant difference in retinal detachment, ROP recurrence, mortality and cerebral palsy between standard treatment and antiVEGF therapy. Subgroup meta-analysis also revealed no statistically significant difference of recurrence of ROP with IVB compared to standard treatment.

The included studies which assessed lower doses of intravitreal antiVEGF (IVB and IVR) for type 1 ROP revealed no statistically significant difference in recurrence of ROP and adverse effects. A meta analysis showed no statistically significant difference in recurrence of ROP with 0.1mg IVR compared to 0.2mg IVR. The data was incomplete to analyse dose response and frequency of injections with different dose of antiVEGF.

Two randomised controlled trials reported significantly higher occurrence of myopia with laser treated group[24, 26]. One comparative trial revealed significantly lower spherical equivalent (more myopic) with either treatment (IVB/laser) treatment in infants with posterior ROP compared to peripheral zone II ROP [36].

There were no serious local or systemic adverse effects reported with standard treatment and antiVEGF treatment. However, the amount of data reported were not sufficient to perform a meta-analysis.

Quality of Evidence

Quality of evidence was measured according to GRADE method. We used GRADE pro GDT platform to analyse data according to the GRADE method[43]. Quality was varied from moderate to very low depending on the type of analysis.

Three meta analyses of retinal detachment in antiVEGF VS standard treatment, recurrence of ROP 0.1mg IVR vs 0.2mg IVR and recurrence of ROP in IVB vs standard treatment gave moderate quality evidence. One meta analysis on recurrence of ROP with antiVEGF vs standard treatment gave low quality of evidence. Two meta analyses of cerebral palsy in antiVEGF vs standard treatment and mortality in antiVEGF vs standard treatment) gave very low-quality evidence.

Figures 2, 4, 6, 8, 10 and 12 illustrate summary of findings and certainty of evidence for all the meta-analysis performed. Majority of included studies, outcome assessment was not masked leading to significant risk of detection bias. None of the included studies have masked the caregivers. Masking of care givers to the treatment is not easily plausible due to the nature of interventions. It is also difficult to predict the impact of masking/unmasking of caregivers on treatment outcomes.

Overall completeness and applicability of evidence

The main objective of this review is to assess the safety and efficacy of intravitreal antiVEGF agents when used either as monotherapy, or in combination with laser photocoagulation in preterm infants with type 1 ROP. This review did not identify studies which assessed outcomes of combination therapy vs standard treatment. Hence, our review has failed to comment on outcomes of combination of treatment with standard treatment.

This review has shown no difference in recurrence of ROP with antiVEGF therapy compared to standard treatment. But the quality of evidence was low (Figure 4). Subgroup analyses revealed no difference of recurrence of ROP with IVB compared to standard therapy with moderate quality of evidence (Figure 5). Thus, we can say with reasonable confidence that recurrence of ROP with antiVEGF is comparable to standard treatment. This statement is important for current practice as this

confirms the finding by Wang et al. in their recent meta-analysis[44]. All other previous meta-analyses didn't have sufficient data to give a conclusion on this matter[8].

In addition, this review found no difference in retinal detachments with antiVEGF compared to standard treatment with moderate quality of evidence. This finding also has a strong addition to current knowledge pool as only one study able to confirm this statement before[8]. This study compared pegaptanib with standard treatment. Our systematic review compared currently used most common antiVEGF agents with standard treatment. Pegaptanib is not included in our study as it is not currently used in most of the institutions.

Major limitations

This systematic review did not analyse data according to the zone of ROP. We realise this is an important subgroup analysis as outcomes can change depending on the zone of ROP. As an example, a comparative study revealed significantly lower spherical equivalent with IVB treatment in infants with posterior ROP compared to peripheral zone II ROP[36].

Majority of included studies had slightly different inclusion criteria for zone of ROP. Thus, we were not able to do a subgroup analysis due to inadequate and highly variable data. We believe this was a major limitation of this review.

Most RCTs included in this review have not reported about visual loss or blindness in a manner adequate for a meta-analysis. We suspect short period of follow up and practicalities with visual assessment at the young age may have been the reasons for in adequate data on visual acuity.

Agreements and disagreements with other reviews

Sankar et al. in their 2018 systematic review stated that IVB / IVR, when used as monotherapy, reduces the risk of childhood refractive errors but does not reduce the risk of retinal detachment or recurrence of retinopathy of prematurity in infants with type 1 ROP[8]. Our review can agree with the latter statement as our meta analysis also revealed no statistical difference in retinal detachment or recurrence of ROP with antiVEGF treatment compared to standard retreatment (please refer table 2, 4, 6 and 8).

A systematic review in 2015 by Pertl et al. concluded that antiVEGF treatment causes lower rates of myopia[45]. Another systematic review and meta-analysis by Wang et al in 2020 showed a statistically significant difference favouring laser group having higher myopia with significant heterogeneity between studies[44]. Furthermore, Tan et al. in their systematic review and met-analysis stated less myopia and astigmatism with IVB than laser treatment for infants with type 1 ROP[46]. Our review can also agree with reduced risk of refractive errors with antiVEGF monotherapy as shown in multiple included studies. But this review failed to confirm latter finding with a meta analysis as there were not adequate data.

Pertl et al. concluded that there is a reduced risk of recurrence of type 1 ROP with antiVEGF[45]. However, our meta analysis revealed no significant difference in recurrence of ROP. The latter systematic review and meta analysis was mainly based on observational studies and only one RCT was included in it. Thus, we suspect significant bias in that study. But there is a possibility that our results could change if we did a subgroup analysis according to the zone of ROP.

Wang et al. in 2020 concluded recurrence incidence were higher in the anti-VEGF group than the laser group, but the meta-analysis showed no statistically significant difference with significant heterogeneity between studies in accordance with our findings[44].

Wang et al. also showed a statistically significant higher complication rate with laser therapy compared to antiVEGF treatment[44]. This study has not defined how they conclude a complication has occurred which affects interpretation of results. Our study could not perform a statistical analysis on complications rate between standard treatment and antiVEGF therapy as outcome analysis were extremely varied between the studies. But none of the included studies have reported significant difference in terms of complications. Thus, we find difficult to agree with confidence on Wang et al. statement regarding complications.

Potential biases in the review process

We found some outcomes were not reported with adequate data suitable for a meta-analysis. Thus, we could not include several studies in our meta-analysis. Even though we contacted the relevant authors for additional details, none of them replied before we did data analysis.

During our literature search we could not find English language translations of 18 studies. We were able contact 16 authors requesting for relevant English language translations. Only two authors replied and none of them had suitable English language translations.

Implications for practice and research

AntiVEGF agents, when used as monotherapy is non inferior to standard therapy in terms of risk of retinal detachment or recurrence of retinopathy of prematurity in infants with type 1 ROP. AntiVEGF monotherapy may reduce the risk of refractive errors in childhood compared to standard therapy. There is no significant risk of cerebral palsy or mortality in infants treated with antiVEGF compared to laser / cryo therapy. No significant risk of acute and long-term systemic complications noted with antiVEGF therapy. None of the included studies reported higher risk of local complications with antiVEGF monotherapy.

However, the quality of evidence was moderate to very low due to the risk of detection bias and other biases. The data is not sufficient to make strong conclusions favouring routine use of intravitreal anti-VEGF agents as monotherapy in preterm infants with type 1 ROP.

Hence, further RCTs are needed to evaluate the effect of antiVEGF agents, when used as monotherapy or combination therapy with laser / cryo. This review couldn't find a RCT which compared combination treatment with standard treatment for type1 ROP. Thus, there is a timely need of a good quality RCT which compare latter two interventions.

The RCTs should ideally be large multicentre trials with enough sample size to detect a clinically important difference and should have adequate follow up period to detect subacute and delayed systemic effects.

This review found that almost all included studies didn't mask the care givers and only a few studies masked the outcome assessment. Thus, future studies should ensure masking of caregivers and examiners to improve the quality and reliability of evidence.

It may be difficult to do a follow up study for more than 2-3 years due to operational reasons. Thus, it will be a good initiative to maintain a registry of infants treated with antiVEGF agents to follow up them long-term to detect rare late implications of therapy.

This review has found highly variable inclusion criteria for zone of ROP in the included studies. Most studies have presented data without separating them according to zones and stages of ROP. This makes difficult to categorise data and perform subgroup meta analysis. We believe high heterogeneity noted in some of the meta analyses were due to inclusion of multiple closely related groups in the same meta analysis. Thus, we suggest researchers to present data according to the zones and stages of ROP so that it will be beneficial for future more accurate meta analysis.

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