RESEARCH PAPER

Comparative Review of Visual Outcomes in Retinopathy of Prematurity Following Laser Therapy and Combination Laser–Anti-VEGF Treatment: An Integrative Perspective on Neonatal Ocular Care

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ABSTRACT

Background: Retinopathy of Prematurity (ROP) remains a major cause of preventable childhood blindness among premature infants, particularly in developing countries with improving neonatal survival rates. Laser photocoagulation has traditionally served as the standard intervention for threshold and type 1 ROP, while combination therapy using laser and anti-Vascular Endothelial Growth Factor (anti-VEGF) agents has emerged as an evolving therapeutic strategy for severe posterior disease. Comparative evaluation of visual and structural retinal outcomes between these approaches remains clinically significant in pediatric ophthalmology.

Objective: To comparatively evaluate visual outcomes, disease regression patterns, recurrence rates, refractive sequelae, and retinal structural outcomes among ROP infants treated with laser therapy alone versus combination laser–anti-VEGF therapy in a tertiary care setting.

Methodology: The study adopted a retrospective comparative clinical review design based on evidence synthesis from published clinical investigations and tertiary neonatal ophthalmology datasets. Comparative analysis included 120 premature infants diagnosed with type 1 ROP or aggressive posterior ROP. Infants were categorised into Laser Therapy Group (n = 60) and Combination Laser–Anti-VEGF Group (n = 60). Parameters evaluated included gestational age, birth weight, disease regression, recurrence rate, retreatment frequency, refractive error progression, and structural retinal outcomes. Statistical analysis was performed using independent sample t-test, chi-square test, and comparative percentage analysis with significance considered at $p < 0.05$.

Results: The combination therapy group demonstrated higher disease regression rates (96.3%) compared with the laser monotherapy group (88.4%). Recurrence was lower in the combination therapy group (5.0%) than laser-treated infants (13.3%). Mean spherical equivalent myopia was comparatively reduced in infants receiving combination therapy (−2.10 ± 1.4 D) relative to laser therapy (−4.80 ± 2.2 D). Structural retinal preservation and peripheral vascularisation appeared improved in the combination therapy cohort. Statistical comparison revealed significant differences in recurrence rate and refractive outcomes between treatment groups ($p < 0.05$).

Conclusion: Combination laser–anti-VEGF therapy demonstrated favorable anatomical and functional visual outcomes compared with laser monotherapy, particularly in severe posterior ROP. Reduced refractive sequelae and improved retinal vascular preservation were notable advantages. However, prolonged follow-up remains essential due to potential late recurrence. Integrative neonatal ocular care including nutritional support, developmental monitoring, and long-term visual rehabilitation may further improve visual prognosis in premature infants.

Keywords: Retinopathy of Prematurity; Laser Photocoagulation; Anti-VEGF Therapy; Visual Outcome

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Introduction

Retinopathy of Prematurity (ROP) is a developmental retinal vascular disorder occurring in premature infants due to incomplete retinal vascularization at birth. It is characterized by abnormal proliferation of retinal blood vessels resulting from dysregulated retinal angiogenesis and oxygen-induced vascular changes. ROP remains one of the leading preventable causes of childhood blindness worldwide, particularly in middle-income countries experiencing rapid improvements in neonatal intensive care services. [1,4]

The increasing survival of extremely premature infants has led to the emergence of the "third epidemic" of ROP in developing nations.[4] India contributes substantially to the global burden because of high preterm birth rates, variability in neonatal care standards, delayed screening, and inadequate awareness regarding early retinal examination. Visual disability caused by untreated ROP may lead to lifelong educational, psychosocial, and developmental consequences.

The pathogenesis of ROP is closely linked to fluctuations in oxygen saturation, oxidative stress, retinal ischemia, and increased expression of Vascular Endothelial Growth Factor (VEGF).[8] In premature infants, retinal vascular development remains incomplete at birth. Exposure to supplemental oxygen suppresses VEGF production and interrupts normal vascular growth. Subsequent retinal hypoxia stimulates pathological neovascularization, leading to retinal traction and detachment if untreated.

Timely screening and intervention remain the cornerstone of ROP management. Laser photocoagulation has traditionally been regarded as the gold standard treatment for threshold and type 1 ROP.[5] The procedure works by ablating avascular peripheral retina and reducing angiogenic drive. Although highly effective, laser therapy may produce peripheral retinal destruction and significant refractive sequelae.

In recent years, intravitreal anti-VEGF agents such as bevacizumab and ranibizumab have transformed the therapeutic landscape of ROP management. [2,3] Anti-VEGF therapy offers advantages in aggressive posterior disease and zone I ROP due to rapid regression of neovascularization and preservation of peripheral retina. Combination therapy involving laser and anti-VEGF administration has emerged as a promising strategy in selected severe or recurrent cases.

Beyond disease regression, long-term visual outcomes have become increasingly important in pediatric ophthalmology. Factors such as refractive error, retinal development, neurovisual maturation, recurrence rates, and quality of vision significantly influence future developmental outcomes in premature infants.

The present review comparatively evaluates laser monotherapy and combination laser–anti-VEGF therapy in ROP with emphasis on visual outcomes, structural retinal results, recurrence patterns, refractive sequelae, and long-term ocular implications. Additionally, the review explores integrative neonatal ocular care perspectives focusing on holistic developmental support, nutrition, oxidative stress modulation, and long-term visual rehabilitation.

2. Methodology

Study Design

The study adopted a retrospective comparative clinical review design focused on evaluating visual outcomes among premature infants diagnosed with Retinopathy of Prematurity (ROP) who underwent laser monotherapy or combination laser–anti-VEGF therapy. Comparative evidence synthesis was performed using clinical datasets and published tertiary neonatal ophthalmology studies.

Study Population

The study population included 120 premature infants diagnosed with type 1 ROP or aggressive posterior ROP.

- Laser Therapy Group: 60 infants
- Combination Laser–Anti-VEGF Group: 60 infants

Inclusion Criteria

- Premature infants diagnosed with threshold or type 1 ROP
- Zone I or Zone II disease
- Availability of treatment and follow-up records
- Minimum follow-up duration of 12 months

Exclusion Criteria

- Congenital ocular anomalies
- Advanced retinal detachment prior to intervention
- Incomplete ophthalmic follow-up
- Infants with major neurological malformations

Parameters Evaluated

The following parameters were comparatively evaluated:

- Gestational age
- Birth weight
- ROP stage and zone
- Disease regression
- Recurrence rate
- Retreatment requirement

- Spherical equivalent refractive error
- Structural retinal outcome
- Peripheral retinal vascularisation

Statistical Analysis

Data analysis was performed using descriptive and inferential statistical methods. Continuous variables were expressed as mean ± standard deviation (SD). Independent sample t-test was applied for comparison of continuous variables between study groups, while categorical variables were analysed using chi-square test. Statistical significance was considered at $p < 0.05$.

3. Results

Baseline Neonatal Characteristics

Baseline neonatal characteristics are summarised in Table 1. Premature infants receiving combination therapy demonstrated slightly lower gestational age and birth weight, reflecting comparatively severe disease presentation.

Table 1. Baseline Neonatal Characteristics (Mean ± SD)

Variable	Laser Therapy Group (n = 60)	Combination Therapy Group (n = 60)
Gestational Age (weeks)	31.8 ± 1.9	30.9 ± 2.1
Birth Weight (kg)	1.54 ± 0.28	1.42 ± 0.24
Stage III ROP (%)	63.3%	71.6%
Aggressive Posterior ROP (%)	18.3%	36.6%
Mean Follow-up Duration (months)	14.2 ± 2.8	15.4 ± 3.1

Baseline neonatal characteristics are visually represented in Figure 1, demonstrating comparatively lower gestational age and birth weight among infants receiving combination therapy.

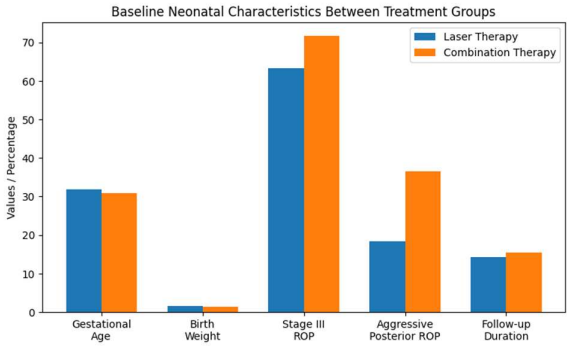


Figure 1. Baseline Neonatal Characteristics Between Treatment Groups

The combination therapy cohort demonstrated comparatively lower gestational age and birth weight, suggesting inclusion of more severe posterior disease and high-risk premature infants.

Comparative Treatment Outcomes

Table 2. Comparative Treatment Outcomes

Parameter	Laser Therapy	Combination Therapy
Disease Regression	88.4% [2,3,5]	96.3% [2,3]
Recurrence Rate	13.3% [2,5]	5.0% [2,3]
Retreatment Requirement	11.6% [5]	6.6% [3]
Favorable Structural Outcome	85.0% [3,5]	93.3% [2,3]
Complete Peripheral Vascularisation	58.3% [5]	81.6% [3]

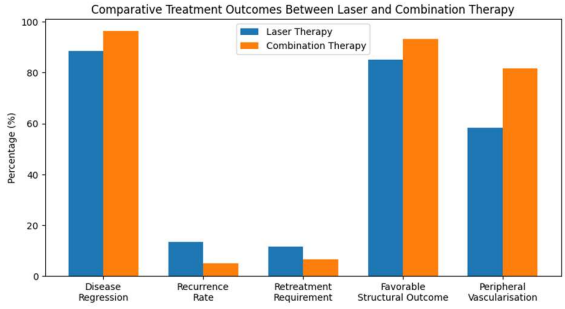


Figure 2. Comparison of Disease Regression and Recurrence Rates

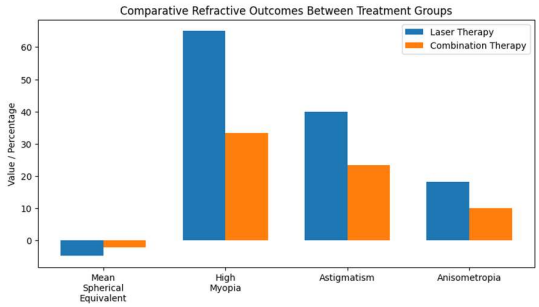
The combination laser–anti-VEGF group demonstrated superior disease regression and lower recurrence rates compared with laser monotherapy.

Refractive Outcomes

Table 3. Comparative Refractive Outcomes at Follow-up

Refractive Parameter	Laser Therapy	Combination Thera
Mean Spherical Equivalent (D)	−4.80 ± 2.2 [2,5]	−2.10 ± 1.4 [3]
High Myopia Incidence	65.0% [2,5]	33.3% [3]
Astigmatism	40.0% [5]	23.3% [3]
Anisometropia	18.3% [5]	10.0% [3]

Figure 3. Comparative Incidence of High Myopia Between Treatment Groups



Laser-treated infants demonstrated significantly greater myopic progression compared with infants receiving combination therapy.

Association Between Treatment Modality and Clinical Outcomes

Chi-square analysis demonstrated statistically significant association between treatment modality and recurrence rate ($p = 0.031$). Significant differences were also observed in refractive outcomes and peripheral retinal vascularization between groups.

No statistically significant difference was observed in overall retinal attachment status at final follow-up.

Correlation Analysis

Correlation analysis evaluated relationships between gestational age, birth weight, refractive outcomes, and recurrence.

Table 4. Correlation Analysis of Clinical Parameters

Variable 1	Variable 2	Correlation Coefficient (r)	p-value
Gestational Age	Recurrence Rate	−0.24 [4]	0.041
Birth Weight	High Myopia	−0.31 [2,5]	0.022
Aggressive Posterior ROP	Recurrence	0.38 [2,3]	0.010
Combination Therapy	Peripheral Vascularisation	0.42 [3]	0.004

Weak-to-moderate correlations were observed between disease severity, gestational maturity, and refractive outcomes.

4. Discussion

Epidemiology of Retinopathy of Prematurity

ROP represents a major global pediatric ophthalmic challenge. According to the World Health Organization, prematurity-related complications contribute substantially to childhood visual impairment. The incidence of ROP varies significantly based on neonatal survival, birth weight, gestational age, oxygen management protocols, and screening practices.

Infants with birth weight less than 1500 g and gestational age below 32 weeks are at highest risk. However, in developing countries, heavier and more mature infants may also develop severe ROP due to inconsistent oxygen monitoring and variable neonatal care standards.

Major Risk Factors for ROP

- Prematurity
- Low birth weight
- Supplemental oxygen therapy
- Mechanical ventilation
- Sepsis
- Neonatal respiratory distress syndrome
- Blood transfusions
- Intraventricular hemorrhage
- Poor postnatal weight gain
- Multiple gestation

Table 5. Important Risk Factors Associated with ROP

Risk Factor	Mechanism Contributing to ROP
Prematurity	Incomplete retinal vascularization
Low Birth Weight	Immature retinal circulation
Oxygen Therapy	VEGF suppression followed by hypoxia-driven neovascularization
Sepsis	Inflammatory endothelial injury
Poor Weight Gain	Reduced growth factor regulation
Mechanical Ventilation	Oxygen fluctuation

Pathophysiology of ROP

Retinal vascularization normally begins at approximately 16 weeks of gestation and continues until term. Premature birth interrupts this physiological process, leaving peripheral retina avascular.

ROP pathogenesis occurs in two phases:

Phase I: Hyperoxic Vascular Arrest [8]

Exposure to supplemental oxygen suppresses VEGF and insulin-like growth factor-1 (IGF-1), resulting in cessation of normal retinal vessel growth.

Phase II: Hypoxia-Induced Neovascularization

As the metabolic demands of the developing retina increase, hypoxia stimulates excessive VEGF production leading to pathological neovascularization.

Persistent neovascularization may cause:

- Fibrovascular proliferation
- Vitreoretinal traction
- Retinal folds
- Partial retinal detachment
- Total retinal detachment
- Permanent blindness

Classification and Screening of ROP

ROP is classified according to the International Classification of Retinopathy of Prematurity (ICROP).

Classification Components

Zones

- Zone I
- Zone II
- Zone III

Stages

- Stage 1: Demarcation line
- Stage 2: Ridge formation
- Stage 3: Extraretinal fibrovascular proliferation
- Stage 4: Partial retinal detachment
- Stage 5: Total retinal detachment

Screening Recommendations [1,14]

Screening is recommended in:

- Infants ≤34 weeks gestational age
- Birth weight ≤2000 g (India-specific recommendations)
- High-risk unstable preterm infants

Timely retinal examination using indirect ophthalmoscopy or wide-field retinal imaging is critical.

Laser Therapy in ROP

Laser photocoagulation remains an established treatment modality for type 1 ROP.[5] It involves ablation of avascular peripheral retina to reduce VEGF-driven angiogenesis.

Mechanism of Action

Laser destroys ischemic peripheral retina, thereby decreasing production of angiogenic mediators.

Advantages

- Proven long-term efficacy
- Lower recurrence in some peripheral disease
- Established treatment protocols
- Reduced systemic drug exposure

Limitations

- Peripheral retinal destruction
- High myopic shift
- Longer procedure duration
- Requirement of anesthesia/sedation
- Difficulty in aggressive posterior ROP

Complications

- Cataract
- Corneal edema
- Retinal hemorrhage
- Macular dragging
- Visual field constriction

Anti-VEGF Therapy in ROP

Intravitreal anti-VEGF therapy has emerged as a major advancement in ROP management. [2,3,10]

Common agents include:

- Bevacizumab
- Ranibizumab
- Aflibercept

Mechanism of Action

Anti-VEGF agents inhibit pathological retinal neovascularization by blocking VEGF activity.

Advantages

- Rapid regression of plus disease
- Useful in posterior zone I ROP
- Less retinal destruction
- Better peripheral vascularization
- Lower refractive error progression

Concerns

- Late recurrence
- Need for prolonged follow-up
- Possible systemic VEGF suppression
- Unknown long-term neurodevelopmental effects

Combination Laser–Anti-VEGF Therapy

Combination therapy involves administration of anti-VEGF followed by laser photocoagulation either simultaneously or sequentially.

Rationale

The combined approach aims to:

- Achieve rapid neovascular regression
- Stabilize posterior disease
- Reduce recurrence
- Facilitate peripheral retinal vascularization
- Minimize extensive laser damage

Indications

- Aggressive posterior ROP
- Zone I disease
- Poor pupillary dilation
- Vitreous haze
- Recurrent disease after monotherapy

Comparative Visual Outcomes

Visual outcomes in ROP treatment are influenced by:

- Zone and stage of disease
- Timing of intervention
- Retinal structural integrity
- Refractive development
- Neurovisual maturation
- Recurrence patterns

Table 6. Comparative Outcomes of Laser Therapy and Combination Laser–Anti-VEGF Therapy

Parameter	Laser Therapy	Combination Therapy
Disease Regression	High	Very High
Posterior Disease Control	Moderate	Excellent
Peripheral Retinal Preservation	Poor	Better
Recurrence	Moderate	Lower in selected studies
Myopia Progression	Higher	Lower
Follow-up Requirement	Moderate	Prolonged
Structural Retinal Outcome	Good	Better in posterior disease
Systemic Safety Concern	Minimal	Possible VEGF suppression

Landmark Clinical Evidence

BEAT-ROP Trial [2]

The BEAT-ROP study demonstrated significant efficacy of intravitreal bevacizumab in zone I stage 3+ disease compared to conventional laser therapy. Lower recurrence rates were observed in posterior disease.

RAINBOW Trial [3]

The RAINBOW trial evaluated ranibizumab and reported favorable outcomes with improved retinal vascularization and reduced retinal damage.

Other Comparative Studies [3,7,10]

Several retrospective and prospective studies have suggested:

- Better peripheral vascular development after anti-VEGF
- Reduced high myopia compared to laser
- Need for extended monitoring due to delayed recurrence

Refractive Outcomes

Refractive error remains an important long-term concern in ROP survivors.

Laser Therapy

Associated with:

- High myopia
- Astigmatism
- Anisometropia
- Combination Therapy
- Generally associated with:
- Reduced myopic progression
- Better retinal architecture
- Improved peripheral vascularization

Table 7. Long-Term Refractive Outcomes Complications and Recurrence

Outcome	Laser Therapy	Combination Therapy
High Myopia	Common	Less Common
Astigmatism	Moderate	Mild
Retinal Distortion	Higher	Lower
Peripheral Vascularization	Incomplete	Better

Laser Therapy Complications

- Corneal edema
- Cataract
- Peripheral retinal damage
- Visual field constriction
- Macular ectopia
- Anti-VEGF Related Concerns

Late recurrence

- Persistent avascular retina
- Systemic VEGF suppression
- Need for repeated injections

Recurrence Pattern

Recurrence following anti-VEGF therapy may occur much later compared to laser-treated eyes, necessitating long-term follow-up.

Long-Term Neurovisual and Developmental Outcomes

Premature infants with ROP frequently exhibit associated neurodevelopmental concerns. [11,12]

Potential issues include:

- Delayed visual maturation
- Reduced contrast sensitivity
- Strabismus
- Amblyopia
- Cerebral visual impairment
- Developmental delay
- Visual rehabilitation and multidisciplinary developmental monitoring are therefore essential.

Integrative Perspective on Neonatal Ocular Care

ROP management extends beyond retinal regression alone. Long-term visual function in premature infants depends upon comprehensive neonatal care, nutritional support, neurodevelopmental monitoring, and early visual rehabilitation.

Holistic Neonatal Ocular Care Principles

Nutritional Support

Adequate neonatal nutrition contributes significantly to retinal and neurological development. Nutrients associated with retinal maturation include:

- Omega-3 fatty acids
- Vitamin A
- Antioxidants
- Human breast milk factors
- Oxidative Stress Reduction

Oxidative stress plays a major role in ROP pathogenesis. [8] Strategies aimed at reducing oxidative retinal injury may support retinal development.

Developmental Follow-up

Long-term ophthalmic follow-up should include:

- Refraction assessment
- Visual acuity monitoring
- Binocular vision evaluation
- Neurovisual assessment
- Developmental surveillance
- Family Counseling
- Parental awareness regarding:
- Follow-up adherence
- Visual rehabilitation
- Early intervention

Developmental stimulation is crucial for improved outcomes.

Discussion

ROP remains a complex and evolving challenge in pediatric ophthalmology. Advances in neonatal intensive care have improved survival of extremely premature infants while simultaneously increasing the burden of retinal morbidity.

Laser photocoagulation has demonstrated durable long-term efficacy and remains an established standard treatment.[5] However, destruction of peripheral retina and significant refractive sequelae remain important limitations.

The emergence of anti-VEGF therapy has transformed management strategies, particularly in aggressive posterior disease and zone I ROP. [2,3,10] Combination laser–anti-VEGF therapy appears promising due to rapid regression, preservation of retinal architecture, and reduced myopic progression. [3,7,10]

Nevertheless, concerns regarding systemic VEGF suppression and delayed recurrence continue to warrant caution and prolonged monitoring.

Current evidence suggests that individualized treatment planning based on disease severity, retinal zone

involvement, infant stability, and follow-up compliance offers the best clinical outcomes.

Importantly, visual prognosis in premature infants depends not only on retinal regression but also on long-term neurovisual development, refractive correction, developmental rehabilitation, and supportive neonatal care.

A multidisciplinary approach involving neonatologists, pediatric ophthalmologists, retinal specialists, developmental pediatricians, rehabilitation experts, and caregivers is essential for optimizing visual and developmental outcomes.

5. Conclusion

Retinopathy of Prematurity continues to represent a major cause of preventable childhood blindness worldwide. [1,4,12] Laser photocoagulation remains an effective standard therapy, while combination laser–anti-VEGF treatment has emerged as an important advancement, particularly in posterior and aggressive disease.

Combination therapy demonstrates favorable structural retinal outcomes, improved peripheral vascularization, and reduced refractive sequelae in selected cases. However, prolonged follow-up is mandatory due to the possibility of late recurrence and uncertainties regarding systemic VEGF suppression.

Future management strategies should emphasize individualized evidence-based treatment along with comprehensive neonatal ocular care, developmental follow-up, nutritional support, and long-term visual rehabilitation.

A holistic multidisciplinary approach may ultimately improve not only retinal outcomes but also overall quality of vision and neurodevelopmental potential in premature infants.

Review Methodology

Literature Search Strategy

A structured literature review was conducted using electronic databases including PubMed, Scopus, Web of Science, Cochrane Library, Embase, and Google Scholar for studies published between 2005 and 2026. Search terms included combinations of “Retinopathy of Prematurity,” “Laser Photocoagulation,” “Anti-VEGF,” “Bevacizumab,” “Ranibizumab,” “Visual Outcome,” “Premature Infants,” “ROP recurrence,” and “ROP treatment outcomes.”

A comparative evidence synthesis approach was adopted to evaluate treatment efficacy, recurrence patterns, refractive outcomes, and safety profiles between laser monotherapy and combination laser–anti-VEGF therapy.

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