• Clinical Research •

Impact of different treatment approaches on long-term refractive and visual outcomes in retinopathy of prematurity

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Abstract

● **AIM:** To evaluate the long-term refractive and visual outcomes in infants with retinopathy of prematurity (ROP) treated with intravitreal bevacizumab (IVB), laser photocoagulation (LPC), or combined IVB+LPC therapy, and to assess disease severity on refractive development over five years.

● **METHODS:** This retrospective cohort study analyzed data from infants diagnosed with ROP between 2013 and 2018. Patients were categorized into four groups: IVB (*n*=44), LPC (*n*=41), IVB+LPC (*n*=17), and regressed ROP (RROP, *n*=50). A subgroup analysis was performed for Type 1 ROP and aggressive ROP (AROP). Primary outcomes included spherical equivalent (SE), astigmatism, and visual acuity (logMAR), measured at 6-month intervals up to 60mo.

● **RESULTS:** The study included 152 patients (76 females). The mean birth weight was 1256.1±555.6 g, and the mean week of birth was 29.1±2.9wk. RROP infants had the highest SE, closest to emmetropia. The IVB+LPC group showed the most significant myopic shift compared to other groups (P<0.05). In Type 1 ROP, SE was lower in the IVB+LPC group initially, but by 60mo, the difference was not significant. Astigmatism was higher in the LPC group at later time points (36–60mo). However, no differences in visual acuity were observed at the final follow-up among treatment groups.

● **CONCLUSION:** Refractive outcomes vary more in Type 1 ROP than AROP. IVB+LPC results in greater myopia; LPC is associated with increased astigmatism. Individualized refractive follow-up is essential, particularly for Type 1 ROP.

● **KEYWORDS:** retinopathy of prematurity; refractive error; regressed retinopathy of prematurity; intravitreal bevacizumab; laser photocoagulation

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INTRODUCTION

Retinopathy of prematurity (ROP) is a vascular abnormality in pre-term infants that can cause permanent visual impairment if not treated early[1]. It is one of the leading causes of childhood blindness worldwide, particularly in moderate and high-income countries[2]. Conventional therapies for ROP include diode laser photocoagulation (LPC), and cryotherapy[3]. Intravitreal anti vascular endothelial growth factor (VEGF) agents such as intravitreal bevacizumab (IVB) have shown promising results and may be advantageous when Zone I is involved[4].

Beyond structural success, ROP survivors face substantial refractive morbidity. High myopia, astigmatism, and anisometropia are common and drive amblyopia risk and long-term functional vision loss[5]. Significant refractive errors are reported to be several-fold more frequent in ROP than in the general pediatric population[6]. Additionally, the modality of treatment appears to influence the pattern of refractive development; for example, cryotherapy has been linked to higher myopia, astigmatism, and anisometropia[6-7]. Yet the literature remains mixed and often short-term, with limited stratification by disease severity and with few cohorts directly comparing IVB, LPC, and IVB+LPC.

Accordingly, this study evaluates long-term changes in spherical equivalent (SE), astigmatism, and visual acuity over 5y in infants with ROP managed with IVB, LPC, or IVB+LPC, with subgroup analyses by disease severity. Our goal is to provide evidence that informs treatment selection and post-treatment refractive care to reduce amblyopia risk and optimize childhood visual outcomes.

PARTICIPANTS AND METHODS

Ethical Approval The study was approved by the Ethical Committee of Zeynep Kamil Maternity and Children's Disease Training and Research Hospital (Approval Number: 151/08.11.2023). The study was conducted according to the Declaration of Helsinki and written informed consent was obtained from the parents of all participants.

Patient Selection and Treatment Group Subdivisions This study included patients diagnosed with ROP at different stages. The medical records of all infants followed for ROP were reviewed. Individuals were included if cycloplegic refraction had been performed and treatment-related clinical data were complete. Cases with disorders associated with abnormal refractive development—or in whom reliable refraction could not be obtained—were excluded, including glaucoma, aphakia, microphthalmia, retinal detachment, and persistent hyperplastic primary vitreous. When both eyes had ROP, the eye with the more severe ROP was included in the study.

All patients were followed up for at least 5y after diagnosis, with follow-up visits at 6-month intervals up to 60mo. We classified patients retrospectively according to the recent updated international classification of ROP (ICROP 3) into: aggressive ROP (AROP) which is a severe, progressive form of ROP in zone I or zone II, and ROP type 1 at which plus disease is present in zone 1 at any stage, stage 3 ROP at zone 1, or stage 2/3 at zone 2 with plus disease[8]. Spontaneous regression was defined as ROP that regressed spontaneously under conservative follow-up without treatment (n=50). Patients with stage 2–3 ROP with plus disease and AROP in zone 1 and posterior zone 2 received IVB treatment (n=44), while patients with persistent peripheral avascular areas after IVB treatment postmenstrual age (PMA) 60wk received LPC treatment (IVB+LPC, n=17). Patients with stage 2–3 plus disease in zone 2, anterior zone 2 and zone 3 received only laser treatment (LPC, n=41).

Demographics, Refraction, Visual Acuity, Strabismus, and Fundus Examinations Collection All demographic data including gender, birth weight, week of birth, treatment applied and its date, and follow-up length were recorded. Visual acuity was evaluated using Lea symbols or Snellen letters. For analysis, visual acuity values were converted to the logarithm of the minimum angle of resolution (logMAR). Regardless of the treatment, children were examined semi-annually for fixation pattern, ocular motility, and development of the anterior and posterior segments, as well as refractive status after complete regression of ROP. Refractive measurements were taken semi-annually from the 6th month up to the 60th month. For cycloplegic refraction, 1% cyclopentolate drops (Sikloplejin, Abdi İbrahim, Istanbul, Türkiye) were administered twice at 10-minute intervals, and refraction was assessed 45–60min later using a handheld autorefractometer (HandyRef-K Kerato-Refractometer, Nidek, Japan) from a distance of 45 mm with the patient either lying supine or sitting upright. Cylinder (D) and SE=sphere+cylinder/2 (D) were recorded. Any strabismus detected at follow-up visits after the 6th month was recorded. Detailed fundus examinations were performed at each visit using indirect ophthalmoscopy. This method allowed for visualization of the retina and assessment of treatment response, including regression of plus disease and neovascularization at each visit.

Treatment Application and Setting IVB was used off label for the treatment of ROP. Prior to injection, the off-label nature of anti-vascular endothelial growth factor therapy, its potential ocular and systemic risks, and alternative treatment options were explained in detail to the parents or legal guardians, and written informed consent was obtained. For IVB, after standard preparation of the eyes and periocular area with 5% povidone-iodine under local anesthesia, 0.500 mg (0.020 mL) bevacizumab (Altuzan 100 mg/4 mL vial, Roche, Türkiye) was injected into the vitreous cavity *via* the pars plicata, approximately 1.5 mm behind the limbus, using a 30-G needle. An experienced nurse assisted in stabilizing the infant during the procedure. Topical antibiotic drops were administered for 5d following the injections.

Regarding LPC, under general anesthesia, retinal photocoagulation was performed using an 810 nm diode laser (Nidek Inc., Japan) to create moderate-intensity grey-white burns. Laser spots were applied in a semi-confluent manner to cover all avascular retina from the stage line to 1-disc diameter beyond the ora serrata. All LPC procedures were conducted under general anesthesia by two experienced ophthalmologists (Kizilay O and Celik G) and were performed once per patient.

Statistical Analysis Data were analyzed using descriptive statistics, including mean, standard deviation, median, minimum, maximum, frequency, and ratio values. The distribution of the variables was measured using the Kolmogorov-Smirnov test. For the analysis of quantitative independent data, analysis of variance (ANOVA; Tukey test), independent sample t-test, Kruskal-Wallis, and Mann-Whitney U tests were used. For independent qualitative data, the Chi-square test was applied, and when Chi-square test conditions were not met, Fischer's test was used. The analyses were conducted using SPSS 27.0 software (IBM Corp., USA). Only

one eye (the more severely affected) per patient was included, as justified above, to avoid intra-individual correlation.

RESULTS

Patient Demographics and Baseline Characteristics The study included 152 patients (76 females and 76 males). The mean birth weight was 1256.1±555.6 g, and the mean week of birth was 29.1±2.9wk. Among these patients, 102 (67.1%) required treatment, where all these patients had plus disease. Among treated patients, Type 1 ROP predominated (78.4%), whereas 22 patients had AROP (21.6%). The overall SE of the study population changed from 1.36±2.40 to −0.38±2.83 at the last follow-up at 60mo. Astigmatism decreased from −1.59±0.70 to −1.20±0.88 at the last follow-up. Strabismus presented in 16.4% of the study population.

Baseline Characteristics and Treatment Timing Among Different Patient Groups Patients were assigned to IVB (n=44), LPC (n=41), IVB+LPC (n=17) and regressed ROP (RROP; n=50). In the RROP group, all eyes were zone II with stage 1 (n=18), stage 2 (n=27) and stage 3 (n=5). Birth weight and week of birth were higher in RROP than in IVB, LPC and IVB+LPC for birth weight (P<0.001, P=0.033, P=0.010, respectively) and for week of birth (P<0.001, P=0.003, P=0.003, respectively). The three treatment groups were otherwise comparable for these perinatal measures. Among the treatment groups, the first treatment occurred later with LPC than with IVB and IVB+LPC (P=0.001 and P=0.001, respectively), and timing was similar between IVB and IVB+LPC (P=0.238). The distribution of the first treatment zone, stage and plus disease was similar across IVB, LPC, and IVB+LPC, including first treatment zone for IVB compared with IVB+LPC (P=0.317). The number of laser spots was 593.3±454.8 in IVB+LPC and 1206.6±515 in LPC, with a range of 447 to 2293 for LPC (data not shown). Follow-up duration was longest in LPC (P<0.001). At month 60, visual acuity was better in RROP than in IVB, LPC, and IVB+LPC (P<0.001, P=0.003, P<0.001, respectively). Between the treatment groups, visual acuity was similar for IVB and LPC (P=0.367) and higher in LPC than in IVB+LPC (P=0.046). Strabismus and anisometropia frequencies were similar among the groups (Table 1).

Spherical Equivalent and Astigmatism Comparisons Across Treatment Groups RROP group had the highest SE at every visit, staying closest to emmetropia. The IVB+LPC group showed the greatest myopic shift, with lower SE than the other treatment groups at all follow-ups (P<0.05). LPC had higher SE than IVB and IVB+LPC at 6 and 12mo (P<0.05), but this difference narrowed over time. By 60mo, SE was comparable between IVB and LPC (P>0.05), while IVB+LPC remained more myopic (P<0.05; Table 2).

Astigmatism was higher in IVB+LPC and LPC than in IVB and RROP, with the clearest differences at 48 and 60mo (P<0.05). RROP consistently showed the lowest astigmatism across all visits (P<0.05; Table 2).

Spherical Equivalent, Astigmatism, and Visual Acuity in Type 1 ROP Across Treatment Groups At six and twelve months, LPC showed more hyperopic SE than IVB and IVB+LPC (P<0.05 and P<0.05, respectively). IVB+LPC had the greatest myopic shift at these visits. By twenty-four months, SE remained higher in IVB and LPC than in IVB+LPC (P<0.05 and P<0.05, respectively). At thirty-six, forty-eight, and sixty months, SE was comparable among the three treatment groups (P>0.05), with a non-significant trend toward more myopic SE in IVB and LPC (Table 3, Figure 1).

For astigmatism, groups were similar at six months (P=0.112). At twelve months, LPC exceeded IVB (P=0.034). At twenty-four and thirty-six months, LPC and IVB+LPC were higher than IVB (P<0.05 and P<0.05, respectively). At forty-eight months, differences were not significant (P=0.062). At sixty months, IVB+LPC was higher than the other treatment groups (P=0.048). At the final visit, the visual acuity was comparable among IVB, LPC, and IVB+LPC (P=0.231; Table 3, Figure 1).

Spherical Equivalent, Astigmatism, and Visual Acuity in Aggressive ROP Across Treatment Groups In AROP, SE was broadly similar among IVB, LPC, and IVB+LPC at 6, 12, 24, 36, and 60mo (all P>0.05). Across visits, values were numerically most myopic with LPC and least myopic with IVB+LPC, reaching significance at 48mo where LPC was more myopic than the other groups (P<0.05). By 60mo, mean SE was −1.96 D, −6.88 D, and −0.88 D in IVB, LPC, and IVB+LPC, respectively (Figure 2).

Astigmatism was comparable across groups at all time points (all P>0.05). Numerically, LPC tended to have higher astigmatism and IVB+LPC lower astigmatism over time; at 60mo, mean astigmatism magnitudes were 1.50, 2.25, and 1.63 D for IVB, LPC, and IVB+LPC, respectively. Visual acuity did not differ among the three groups at any visit through 60mo (all P>0.05; Table 4).

DISCUSSION

Our study demonstrated that eyes with spontaneously RROP had refractive errors closest to emmetropia and achieved the best visual acuity outcomes, reflecting the milder nature of their disease. In contrast, treated ROP eyes showed notable refractive changes over the 5-year follow-up. Among treatment modalities, the combined therapy group (IVB+LPC) exhibited the greatest myopic shift and astigmatism progression by 60mo, compared to eyes treated with LPC alone or IVB alone. Notably, this myopic shift in the combined group was more pronounced in the early follow-ups, especially in the Type 1 ROP subset, although differences narrowed over time. By the

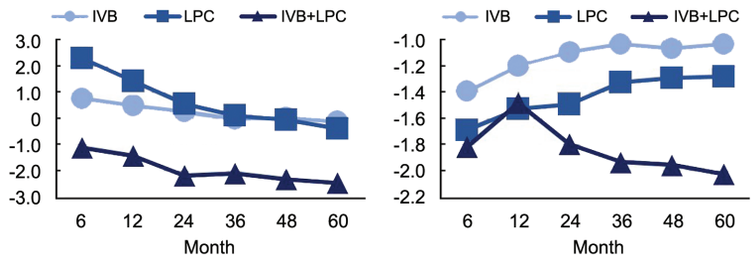

Figure 1 Spherical equivalent and astigmatism changes through type 1 ROP patients among groups IVB: Intravitreal bevacizumab; LPC: Laser photocoagulation; ROP: Retinopathy of prematurity.

Table 1 Comparison of gender, birth weight, birth week, visual acuity, strabismus, and anisometropia across different groups *n* (%)

Variable	IVB[1]	LPC[2]	IVB+LPC[3]	Regressed ROP[4]	*P*	*P* (1 *vs* 2)	*P* (1 *vs* 3)	*P* (1 *vs* 4)	*P* (2 *vs* 3)	*P* (2 *vs* 4)	*P* (3 *vs* 4)
Gender					0.651[b]	0.595	0.763	0.307	0.486	0.649	0.290
Female	20 (45.5)	21 (51.2)	7 (41.2)	28 (56.0)							
Male	24 (54.5)	20 (48.8)	10 (58.8)	22 (44.0)							
Birth weight, g					<0.001[a]	0.562	>0.05	<0.001	0.707	0.033	0.010
Mean±SD	1068±467	1217±463	1055±551	1522±605							
Median	1016.0	1125.0	895.0	1417.5							
Birth week					<0.001[c]	0.270	0.522	<0.001	0.186	0.003	0.003
Mean±SD	28.2±2.7	28.9±2.5	27.7±3.5	30.5±2.7							
Median	28.0	29.0	28.0	31.0							
Treatment week					<0.001[c]	0.001	0.283		0.001		
Mean±SD	35.3±2.4	37.5±2.7	34.8±2.3								
Median	36.0	37.0	34.0								
Treatment zone					0.003[b]	0.005	0.317		<0.001		
I	10 (22.7)	1 (2.4)	6 (35.3)								
II	34 (77.3)	40 (97.6)	11 (64.7)								
Treatment stage					0.514[b]	0.305	0.429		0.963		
II	9 (20.5)	5 (12.2)	2 (11.8)								
III	35 (79.5)	36 (87.8)	15 (88.2)								
Treatment plus					>0.05[b]						
(−)	0	0	0								
(+)	44 (100.0)	41 (100.0)	17 (100.0)								
Type I ROP	32 (72.7)	37 (90.2)	11 (64.7)		0.047[b]	0.039	0.538		0.019		
AROP	12 (27.3)	4 (9.8)	6 (35.3)								
Visual acuity (logMAR)					<0.001[c]	0.367	0.132	<0.001	0.046	0.003	<0.001
Mean±SD	0.08±0.1	0.08±0.1	0.16±0.2	0.01±0.1							
Median	0	0	0.10	0							
Strabismus											
(−)	36 (81.8)	33 (80.5)	13 (76.5)	45 (90.0)	0.474[b]	0.875	0.638	0.252	0.731	0.197	0.158
(+)	8 (18.2)	8 (19.5)	4 (23.5)	5 (10.0)							
Exotropia	2 (4.6)	4 (9.8)	3 (17.6)	2 (4.0)	>0.05[b]	0.302	0.222	>0.05	0.576	0.725	0.524
Esotropia	6 (13.6)	4 (9.8)	1 (5.9)	3 (6.0)							
Anisometropia					>0.05[b]	0.193	>0.05	0.850	0.513	0.247	>0.05
(−)	40 (90.9)	40 (97.6)	16 (94.1)	46 (92.0)							
(+)	4 (9.1)	1 (2.4)	1 (5.9)	4 (8.0)							
Follow-up period, mo					<0.001[c]	<0.001	0.155	0.041	<0.001	<0.001	0.001
Mean±SD	72.9±13.5	92.0±17.9	67.5±8.6	73.9±8.9							
Median	65.5	87.0	65.0	72.0							

[a]ANOVA, [b]Chi-square test, [c]Kruskal-Wallis (Mann-Whitney *U* test). [1]Significant difference with IVB group *P*<0.05; [2]Significant difference with LPC group *P*<0.05; [3]Significant difference with IVB+LPC group *P*<0.05; [4]Significant difference with regressed ROP group. logMAR: Logarithm of the minimum angle of resolution; SD: Standard deviation; IVB: Intravitreal bevacizumab; LPC: Laser photocoagulation; ROP: Retinopathy of prematurity; AROP: Aggressive retinopathy of prematurity; ANOVA: Analysis of variance.

final 5-year visit, refractive outcomes (SE and astigmatism) were statistically comparable among the treated groups in both Type 1 ROP and AROP, suggesting a convergence of refractive error outcomes in the longer term. We also observed that strabismus and anisometropia rates did not differ significantly between the treatment groups, indicating that the choice of treatment modality did not measurably influence these outcomes in our cohort.

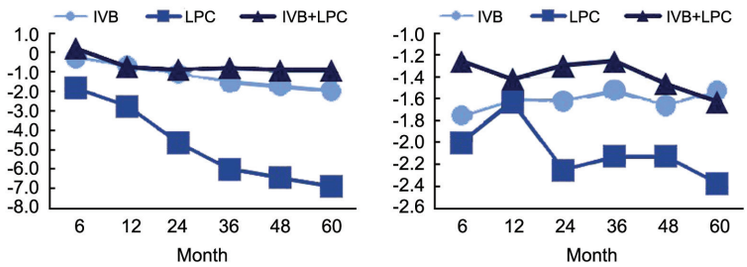

Figure 2 Spherical equivalent and astigmatism changes through aggressive ROP patients among groups IVB: Intravitreal bevacizumab; LPC: Laser photocoagulation; ROP: Retinopathy of prematurity.

Table 2 Spherical equivalent and astigmatism measurements over the study period

Variable	IVB[1]	LPC[2]	IVB+LPC[3]	Regressed ROP[4]	*P*	*P* (1 *vs* 2)	*P* (1 *vs* 3)	*P* (1 *vs* 4)	*P* (2 *vs* 3)	*P* (2 *vs* 4)	*P* (3 *vs* 4)
Spherical equivalent (D)											
6mo					<0.001[c]	0.001	0.075	<0.001	<0.001	0.920	<0.001
Mean±SD	0.48±2.32	1.92±2.56	−0.63±2.41	2.34±1.56							
Median	1.00	2.50	0.50	2.25							
12mo					<0.001[c]	0.021	0.056	<0.001	0.002	0.594	<0.001
Mean±SD	0.18±2.32	1.04±2.52	−1.18±2.87	1.80±1.27							
Median	1.00	2.00	0.50	1.50							
24mo					0.001[c]	0.357	0.142	0.003	0.024	0.159	<0.001
Mean±SD	−0.10±2.40	0.05±2.94	−1.70±3.56	1.39±1.18							
Median	0.75	1.00	0.50	1.25							
36mo					0.006[c]	0.618	0.478	0.002	0.266	0.028	0.009
Mean±SD	−0.43±2.53	−0.46±3.44	−1.62±3.81	1.19±1.16							
Median	0.50	0.50	0.50	1.00							
48mo					0.023[c]	0.829	0.233	0.039	0.461	0.013	0.018
Mean±SD	−0.44±2.57	−0.68±3.41	−1.81±3.85	1.00±1.16							
Median	0.50	0.50	0.75	0.75							
60mo					0.020[c]	0.540	0.233	0.093	0.614	0.003	0.027
Mean±SD	−0.60±2.66	−1.01±3.38	−1.90±3.90	0.86±1.21							
Median	0.50	0.25	−0.50	0.75							
Astigmatism (D)											
6mo					0.357[c]	0.075	0.582	0.366	0.679	0.251	0.907
Mean±SD	−1.49±0.77	−1.72±0.63	−1.62±0.89	−1.58±0.62							
Median	−1.50	−1.75	−2.00	−1.50							
12mo					0.123[c]	0.037	0.419	0.839	0.415	0.037	0.537
Mean±SD	−1.31±0.62	−1.54±0.53	−1.46±0.67	−1.31±0.56							
Median	−1.25	−1.50	−1.00	−1.25							
24mo					0.014[c]	0.003	0.151	0.475	0.848	0.013	0.203
Mean±SD	−1.24±0.80	−1.57±0.70	−1.62±1.10	−1.20±0.58							
Median	−1.00	−1.50	−1.50	−1.00							
36mo					0.035[c]	0.064	0.101	0.753	0.705	0.013	0.045
Mean±SD	−1.16±0.64	−1.40±0.64	−1.69±1.30	−1.09±0.55							
Median	−1.00	−1.25	−1.25	−1.00							
48mo					0.003[c]	0.231	0.078	0.111	0.198	0.003	0.002
Mean±SD	−1.23±0.74	−1.37±0.76	−1.78±1.30	−0.97±0.55							
Median	−1.00	−1.25	−1.50	−0.75							
60mo					<0.001[c]	0.107	0.027	0.077	0.099	<0.001	<0.001
Mean±SD	−1.16±0.88	−1.38±0.78	−1.88±1.33	−0.86±0.55							
Median	−1.00	−1.50	−1.75	−1.00							

[c]Kruskal-wallis (Mann-Whitney *U* test). [1]Significant difference with IVB group *P*<0.05; [2]Significant difference with LPC group *P*<0.05; [3]Significant difference with IVB+LPC group *P*<0.05; [4]Significant difference with regressed ROP group. SD: Standard deviation; IVB: Intravitreal bevacizumab; LPC: Laser photocoagulation; ROP: Retinopathy of prematurity; D: Diopter.

Table 3 Spherical equivalent, astigmatism, and visual acuity in type 1 ROP patients among treatment groups

Variable	IVB[1]	LPC[2]	IVB+LPC[3]	*P*	*P* (1 *vs* 2)	*P* (1 *vs* 3)	*P* (2 *vs* 3)
Spherical equivalent (D)							
6mo				<0.001[c]	<0.001	0.021	<0.001
Mean±SD	0.76±1.90	2.32±2.15	−1.11±2.57				
Median	0.88	2.75	−1.50				
12mo				0.001[c]	0.008	0.027	0.001
Mean±SD	0.48±1.86	1.45±2.14	−1.43±2.92				
Median	1.00	2.00	−1.75				
24mo				0.017[c]	0.216	0.043	0.005
Mean±SD	0.27±1.90	0.56±2.43	−2.17±3.79				
Median	0.88	1.50	−1.25				
36mo				0.193[c]	0.477	0.205	0.071
Mean±SD	−0.02±2.01	0.14±2.74	−2.09±4.19				
Median	0.50	0.75	−1.50				
48mo				0.172[c]	0.871	0.068	0.094
Mean±SD	0.04±2.05	−0.05±2.66	−2.32±4.25				
Median	0.50	0.75	−1.50				
60mo				0.213[c]	0.613	0.083	0.150
Mean±SD	−0.09±1.99	−0.37±2.60	−2.45±4.33				
Median	0.25	0.50	−1.50				
Astigmatism (D)							
6mo				0.112[c]	0.052	0.166	0.693
Mean±SD	−1.39±0.76	−1.69±0.65	−1.82±0.90				
Median	−1.25	−1.75	−2.00				
12mo				0.034[c]	0.009	0.277	0.567
Mean±SD	−1.20±0.57	−1.53±0.56	−1.48±0.76				
Median	−1.00	−1.50	−1.00				
24mo				0.004[c]	0.001	0.048	0.688
Mean±SD	−1.09±0.64	−1.50±0.64	−1.80±1.28				
Median	−1.00	−1.50	−1.50				
36mo				0.029[c]	0.032	0.036	0.255
Mean±SD	−1.03±0.47	−1.32±0.56	−1.93±1.55				
Median	−1.00	−1.25	−1.50				
48mo				0.062[c]	0.095	0.040	0.219
Mean±SD	−1.00±0.56	−1.25±0.65	−2.00±1.57				
Median	−1.00	−1.25	−1.50				
60mo				0.048[c]	0.075	0.038	0.177
Mean±SD	−1.03±0.62	−1.50±0.67	−2.00±1.61				
Median	−0.75	−1.25	−1.50				
Visual acuity (logMAR)				0.231[c]	0.168	0.569	0.151
Mean±SD	0.07±0.10	0.04±0.09	0.14±0.20				
Median	0	0	0				

[c]Kruskal-wallis (Mann-Whitney *U* test). [1]Significant difference with IVB group *P*<0.05; [2]Significant difference with LPC group *P*<0.05; [3]Significant difference with IVB+LPC group *P*<0.05. ROP: Retinopathy of prematurity; SD: Standard deviation; IVB: Intravitreal bevacizumab; LPC: Laser photocoagulation; D: Diopter; logMAR: Logarithm of the minimum angle of resolution.

Our results align with prior studies noting better visual and refractive outcomes in milder, untreated ROP cases. For instance, Park *et al*[9] reported that treated ROP patients (whether by anti-VEGF or laser) had worse visual acuity than those with spontaneously RROP, although there was no significant difference in final vision between different treatment modalities. We similarly found that the ROP-regressed group attained the best visual acuity among all groups, while eyes treated with IVB, LPC, or combined therapy showed no significant difference in final visual acuity from each other in both AROP and Type 1 ROP patients[9].

Recent findings also underscore that visual outcomes after anti-VEGF monotherapy are generally favorable: Wu *et al*[10]

Table 4 Spherical equivalent, astigmatism, and visual acuity in aggressive ROP patients among treatment groups

Variable	IVB[1]	LPC[2]	IVB+LPC[3]	*P*	*P* (1 *vs* 2)	*P* (1 *vs* 3)	*P* (2 *vs* 3)
Spherical equivalent (D)							
6mo				0.611[c]	0.429	0.962	0.285
Mean±SD	−0.27±3.17	−1.81±3.38	0.25±2.00				
Median	1.00	−2.88	1.00				
12mo				0.485[c]	0.223	0.671	0.509
Mean±SD	−0.65±3.20	−2.75±2.87	−0.71±2.98				
Median	1.00	−4.00	0.75				
24mo				0.083[c]	0.052	0.888	0.032
Mean±SD	−1.06±3.29	−4.63±3.47	−0.83±3.23				
Median	0.75	−6.00	1.25				
36mo				0.064[c]	0.051	0.424	0.032
Mean±SD	−1.50±3.44	−6.00±4.79	−0.75±3.14				
Median	0.50	−6.75	1.13				
48mo				0.047[c]	0.044	0.277	0.032
Mean±SD	−1.71±3.41	−6.44±4.61	−0.88±3.13				
Median	0.50	−6.50	1.00				
60mo				0.060[c]	0.067	0.276	0.032
Mean±SD	−1.96±3.71	−6.88±4.50	−0.88±3.05				
Median	0.50	−6.75	0.88				
Astigmatism (D)							
6mo				0.361[c]	0.359	0.393	0.166
Mean±SD	−1.75±0.77	−2.00±0.41	−1.25±0.82				
Median	−1.63	−2.00	−1.25				
12mo				0.749[c]	>0.050	0.533	0.435
Mean±SD	−1.60±0.66	−1.63±0.25	−1.42±0.52				
Median	−1.75	−1.50	−1.25				
24mo				0.286[c]	0.141	0.671	0.197
Mean±SD	−1.63±1.05	−2.25±0.87	−1.29±0.62				
Median	−1.50	−2.25	−1.50				
36mo				0.328[c]	0.221	0.636	0.159
Mean±SD	−1.50±0.88	−2.00±0.93	−1.25±0.55				
Median	−1.75	−2.25	−1.25				
48mo				0.740[c]	0.582	0.635	0.508
Mean±SD	−1.67±0.97	−2.13±1.31	−1.46±0.51				
Median	−1.75	−1.75	−1.50				
60mo				0.627[c]	0.328	0.850	0.516
Mean±SD	−1.50±1.33	−2.25±1.18	−1.63±0.61				
Median	−1.75	−2.00	−1.75				
Visual acuity (logMAR)				0.136[c]	0.104	0.127	0.388
Mean±SD	0.09±0.12	0.35±0.31	0.20±0.17				
Median	0	0.35	0.15				

[c]Kruskal-wallis (Mann-Whitney *U* test). [1]Significant difference with IVB group *P*<0.05; [2]Significant difference with LPC group *P*<0.05; [3]Significant difference with IVB+LPC group *P*<0.05. ROP: Retinopathy of prematurity; SD: Standard deviation; IVB: Intravitreal bevacizumab; LPC: Laser photocoagulation; D: Diopter; logMAR: Logarithm of the minimum angle of resolution.

reported a favorable visual outcome at about 4y post injection with ranibizumab monotherapy in Type 1 ROP.

Jiang *et al*[11] showed in preschool children that laser and anti-VEGF+laser were associated with lower SE (more myopia) and greater astigmatism than anti-VEGF alone, while best corrected visual acuity (BCVA) did not differ among modalities—closely matching our modality-refractive pattern and visual acuity neutrality at five years. This level of vision is comparable to the outcomes in our treated groups and reinforces that early treated ROP eyes, despite suffering some acuity reduction relative to healthy full-term eyes, can achieve functional vision in early childhood.

Our refraction findings are also in line with the broader literature. Numerous studies have shown that infants who undergo ROP treatment develop higher refractive errors (particularly myopia) than those with regression or no ROP[12]. Specifically, laser-treated ROP eyes tend to have a greater myopic shift over time than eyes treated with anti-VEGF agents. Khan and Haider[13] reported that LPC alone led to more severe myopia, whereas eyes treated with IVB (either alone or combined with laser) had a milder myopic outcome.

In our cohort, we observed a similar trend at the 5-year mark: the LPC-only and IVB+LPC groups showed more myopic SE compared to the IVB-only group. However, when stratified by ROP severity (Type 1 *vs* AROP), these differences were not statistically significant at the final follow-up, suggesting that disease severity and time may modulate the initial refractive disparities. Heidary and Gharebaghi[14] reviewed the literature and found contradictory results across studies regarding refractive outcomes of laser *vs* anti-VEGF, attributing the inconsistencies to differences in sample sizes, follow-up durations, and study designs, emphasizing the need for randomized studies to verify these results. Our finding that treated groups ultimately had comparable refractions at 5y—despite earlier deviations—supports the notion that initial differences (due to treatment or disease severity) may diminish as children grow older. It also underlines the importance of long-term follow-up when assessing refractive outcomes in ROP.

Khan and Haider[13] showed that laser treatment alone resulted in higher myopia, while IVB alone or combined with laser treatment resulted in milder myopia. In our study, IVB+LPC and LPC groups showed higher myopic SE at 5y, which was not significantly difference at the last follow-up when sub analysis according to the severity. RROP and IVB showed a moderate myopic trend and were the closest to emmetrope status. Laser-treated eyes with peripheral zone II ROP with advanced treatment age showed no significant myopic shift in comparison to the other eyes[15]. To confirm this, in our study, LPC had the later treatment week that mainly used to treat zone II ROP, and the myopic shift was inferior to the combined therapy (IVB+LPC), although not significant.

Another consideration is the management of residual avascular retina after initial ROP treatment. There is controversy in the literature about whether to proactively laser persistent avascular peripheral retina in infants who received anti-VEGF. Some studies advocate conservative monitoring for late reactivation, while others recommend prophylactic laser ablation of avascular zones to reduce future complications (like traction or recurrence)[16-18]. In our practice, we elected to perform delayed LPC (around 60wk postmenstrual age) to all eyes with remaining avascular retina, aiming to prevent late retinal detachments or reactivations. While this approach standardizes one aspect of management, it also means that many eyes in the IVB monotherapy group eventually received some laser treatment (albeit at a later age under anesthesia). This could attenuate some differences between groups or contribute modestly to refractive outcomes in the IVB-treated eyes. However, given the timing at 60wk, it likely had less impact on refractive development than laser applied at an earlier age (during acute ROP).

Treatment with anti-VEGF injections, such as ranibizumab or bevacizumab, resulted in lower rates of high myopia than laser therapy[17,19-20]. In addition, Isaac *et al*[21] indicated a favorable refractive outcome of a single IVB dose in patients with ROP. Similarly, in our study, the IVB group had a significantly lower myopic shift than the LPC and combined IVB+LPC groups, while these differences were not significant in ROP subtypes among treatment groups.

In the ET-ROP study, the incidence of astigmatism increases in ROP patients where approximately 42% of the included patients developed astigmatism of more than 1 D[22]. In our study, higher astigmatism values at 5y were associated with the LPC and combined IVB+LPC treatment groups, and within the type 1 ROP group (although not significant). Similarly, a recent Meta-analysis by Tan *et al*[23] indicated higher astigmatism values in ROP patients treated with laser in comparison to anti-VEGF agents.

Our data showed no significant difference in strabismus incidence across the regressed and treated groups. Prior research has linked prematurity and severe ROP with higher rates of strabismus (especially esotropia) and abnormal accommodation[24-25]. In particular, severe ROP and high refractive errors (anisometropia or myopia) can predispose to strabismus[12,25]. The absence of a group difference in our study suggests that once ROP is treated successfully, the residual risk of strabismus may be more related to the overall prematurity and neurological status of the child rather than the ROP treatment type. All our patients had plus disease at presentation (indicating significant active ROP), which makes the groups more comparable in baseline risk. It is reassuring that neither anti-VEGF nor laser therapy was associated with a markedly higher strabismus rate in our cohort, and both esotropia and exotropia frequencies were similar between groups[12].

This study has some limitations due to its retrospective nature and being a single-center study. Longer follow-ups (up to 10y) may provide more insights into the effects of these treatment modalities on refractive changes. Despite efforts to collect comprehensive data, there could be unmeasured confounding factors that influence outcomes, such as socioeconomic status and genetic variation. In addition, as the treatment modality was based on the severity of the ROP, the baseline

characteristics might be hard to standardize, however, we did sub analysis for the ROP according to the severity of the case. Furthermore, the imbalance number of patients in AROP among treated groups might affect the reliability of their findings.

The findings of this study highlight the importance of personalized follow-up plans for patients with ROP. Different treatment modalities might have different long-term refractive and visual outcomes. This approach can help to reduce the risk of severe refractive errors and improve overall visual outcomes.

In conclusion, RROP patients showed mild disease, better visual acuity and closer values to emmetropia compared to the treatment groups. Laser treatment, whether combined with IVB or alone, showed the highest myopic shift and astigmatism at month 60, although not significant in the sub analysis. IVB showed moderate refractive changes, but similar final visual acuity compared to laser treatment. Combined treatment patients should be followed up closely to detect any early refraction changes and avoid amblyopia. Future studies should focus on larger cohorts and longer follow-up periods to elucidate the long-term ocular health implications of different ROP treatments.

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