Research Square

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Neurodevelopmental Outcomes of Two Intravitreal Bevacizumab Dosages in Preterm ROP Infants

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Abstract

Purpose

To compare neurodevelopmental outcomes, assessed by Bayley Scales of Infant Development (BSID) and Bayley Infant Neurodevelopmental Screener (BINS) scores, between low-dose and high-dose intravitreal bevacizumab (IVB) in preterm infants treated for retinopathy of prematurity (ROP).

Methods

A retrospective chart review identified infants who received IVB for ROP and completed a BSID (edition 3 or 4) and/or BINS test at a quaternary care pediatric hospital (2011–2024). Patients were divided into high-dose (0.05 mL) and low-dose (0.025 or 0.03 mL) IVB cohorts. BSID/BINS scores and cohort characteristics (gestational age and weight, birth weight, age at injection, age at testing) were compared using t-tests and Fisher exact tests (significance, $p < 0.05$).

Results

Of 89 patients who received IVB, 23 completed a BSID test (10 low-dose, 13 high-dose) and met criteria for analysis. Forty completed at least one BINS subtest. No significant differences were found between dose cohorts for cohort characteristics, all BSID subscores (after p-values were Bonferroni-corrected), any BINS subscore across four age-stratified subtests (3–4, 5–6, 7–10, and 11–15 months), risk-interpretation distributions, or comorbidity distributions.

Conclusions

In unadjusted comparisons of developmental and cohort characteristics, this study found no evidence that lower IVB dosage improves early neurodevelopmental outcomes in preterm infants with ROP. Larger, prospective studies are needed to clarify IVB's neurodevelopmental safety profile.

Introduction

Retinopathy of prematurity (ROP) remains a leading cause of childhood blindness worldwide, affecting preterm infants who have incomplete retinal vascularization.[1,2] Historically, laser photocoagulation was the standard treatment.[3] However, the introduction of intravitreal anti–vascular endothelial growth factor (anti-VEGF) therapy has transformed ROP management, allowing for preserved retinal structure and improved vascularization.[4] Despite the advantages of anti-VEGF therapy, questions persist regarding optimal dosing and potential systemic effects, including neurodevelopmental outcomes in this

vulnerable population. With the FDA approving the first anti-VEGF treatment (aflibercept) for ROP as of February 2023, the possible long-term effects of anti-VEGF treatment remain to be discovered.[5]

Neurodevelopmental outcomes are a central concern when evaluating the systemic safety of anti-VEGF therapy in preterm infants. VEGF plays a critical role in neurogenesis by regulating neuronal migration, axon growth, and neuronal survival.[6] Pharmacokinetic studies have shown that bevacizumab enters the systemic circulation within 24 hours of intravitreal injection and may suppress serum VEGF levels for up to two months.[7] This prolonged systemic suppression has raised concerns that anti-VEGF treatment for ROP could inadvertently affect central nervous system development.[7,8] To assess potential neurodevelopmental effects, studies commonly employ validated developmental assessment tools, including the Bayley Scales of Infant and Toddler Development, edition 3 or 4 (BSID) and the Bayley Infant Neurodevelopmental Screener (BINS) tests.[9] These instruments provide standardized measures of cognitive, motor, and language development during infancy and early childhood, enabling evaluation of potential associations between anti-VEGF exposure and neurodevelopmental outcomes.

Existing studies examining neurodevelopmental outcomes following anti-VEGF treatment have produced inconsistent results.[7,8,10] While one prospective population study found that infants treated with bevacizumab had 3.1 times higher odds of severe neurodevelopmental disabilities and lower BSID motor scores at 18 months compared to those treated with laser photocoagulation,[7] other studies have reported no statistically significant correlation between total bevacizumab dosage and BSID scores at two years.[10] These discrepancies have prompted ongoing investigation into whether anti-VEGF dosing parameters may differentially affect neurodevelopmental outcomes. However, disentangling treatment effects from the effects of prematurity is challenging because birth weight and gestational age are strong independent predictors of ROP severity and subsequent neurodevelopment. The smallest and most premature infants are at greatest risk for severe retinal disease and developmental delay, complicating efforts to isolate treatment-related effects from the underlying consequences of prematurity.[11]

Dose de-escalation studies have explored a wide range of bevacizumab doses for ROP, starting from the standard dose of 0.625 mg (0.025mL) and de-escalating to 0.002 to 0.004 mg (0.00008 to 0.00016 mL).[12,13] While lower doses are hypothesized to reduce systemic VEGF suppression and thereby mitigate neurodevelopmental risk, current evidence has not conclusively demonstrated improved neurodevelopmental outcomes with reduced dosing.[13] This retrospective cohort study aims to compare neurodevelopmental outcomes, as assessed by BSID and BINS scores, across low-dose and high-dose intravitreal bevacizumab (IVB) groups in premature infants treated for ROP, and to examine whether differences in systemic bevacizumab exposure are associated with differences in early neurodevelopmental trajectories.

Methods

A retrospective chart review at a large quaternary care pediatric hospital identified infants who were treated with IVB for ROP and completed BSID III/IV or BINS from 2011 to 2024. Patients were divided into high-dose (0.05mL) and low-dose (0.025mL or 0.03mL) IVB groups based on the total IVB dose administered. The differing dosages implemented reflect the historic practice pattern changes toward reduced dosing per eye, which is consistent with the broader trend in ROP treatment following publication of dose de-escalation studies demonstrating efficacy at doses substantially lower than the original BEAT-ROP standard of 0.625 mg (0.025 mL).[12,13,14]

When comparing baseline characteristics, patients were grouped in broader dose categories (≥ 0.05 mL for high dose and ≤ 0.025 mL for low dose). For BSID and BINS test analysis, high-dose patients only included doses of 0.05 mL; likewise, low-dose patients only included doses of 0.025/0.030 mL. Each patient was classified as unilateral or bilateral based on the eyes treated. BSID scores recorded included cognitive composition (CC), language composition (LC), language receptive communication (LR), language expressive communication (LE), motor composition (MC), fine motor (FM), and gross motor (GM). BINS scores recorded included total score, neurological, receptive communication, expressive communication, and cognitive scores. Gestational age (GA), birth weight (BW), weight at first IVB (WAI), age at injection (AAI), total dosage of IVB administered, dosage of IVB per weight of infant in ml/kg, and age at BSID/BINS test (AT), BSID scores, and BINS scores were recorded and compared between both groups using t-tests.

Due to small sample sizes, Accelerated and Within Normal Limits (WNL) BSID risk score interpretations were combined into a single category, as were Mild Delay and Significant Delay interpretations. No patients received a Moderate Delay BSID interpretation.

BINS tests were categorized by age-specific subtest (3–4, 5–6, 7–10, and 11–15 months). For each visit, the highest age-range subtest completed with sufficient data was recorded. When infants were unable to complete the age-appropriate subtest, a lower age-range subtest was administered to obtain a complete test.

BINS scores yielded interpretations to describe the risk of neurodevelopmental delay in patients. Score interpretations were categorized as high, moderate, or low risk. The number of patients with each score interpretation in each dosage and BINS age range cohort was tabulated. BSID and BINS risk categorical score interpretations, and the distribution of neurodevelopmental, pulmonology, psychiatric, and hearing loss comorbidities present in high and low-dose BSID and BINS cohorts were also compared with chi-squared and Fisher exact tests. The p-value for all statistical tests was set to a significance level of < 0.05. A Bonferroni correction for multiple comparisons was applied to the seven BSID subscores compared (adjusted $\alpha = 0.05/7 = 0.0071$), as this was the main test containing the study's primary findings. Baseline and cohort characteristic comparisons were not formally corrected as these served as checks for similarities between dose groups. P-values for BINS subscore comparisons were not corrected, as none were statistically significant.

Results

Baseline Characteristics of Infants Treated with IVB

A total of 89 patients with ROP who received IVB were identified. Of the 89 patients, 46 patients received a dose of ≥ 0.05 mL and 43 received a dose of ≤ 0.025 mL, and baseline characteristics were similar between both groups (Table 1).

Table 1
Baseline Characteristics Compared Between Patients Who Received > 0.05 mL and < 0.025 mL IVB

Baseline Characteristic	> 0.05mL IVB Patients (n = 46)	< 0.025mL IVB Patients (n = 43)	p-value
Gestational Age (weeks)	24.26 ± 1.02	24.35 ± 1.15	0.70
Birth Weight (kg)	0.66 ± 0.14	0.64 ± 0.17	0.61
Age at Injection (weeks)	35.63 ± 2.78	35.57 ± 2.12	0.90
Weight At Injection (kg)	2.32 ± 0.94	2.13 ± 0.59	0.27

Baseline Characteristics of Infants Who Did And Did Not Receive a BINS or BSID Test

Of the 89 patients, 44 patients completed at least one BSID or BINS test, whereas 45 did not complete either test, and baseline characteristics were similar between both groups (Table 2). 29 completed the BSID, and 40 completed at least one BINS test. Twenty-five patients received both a BSID and at least one BINS test.

Table 2
Baseline Characteristics Compared Between Patients Who Completed ≥ 1 BSID or BINS Test and Patients Who Did Not Complete Any BSID or BINS Test

Baseline Characteristic	Bayley Tested Patients (n = 44)	Untested Patients (n = 45)	p-value
Gestational Age (weeks)	24.23 ± 1.20	24.38 ± 0.96	0.51
Birth Weight (kg)	0.64 ± 0.16	0.66 ± 0.15	0.42
Age at Injection (weeks)	35.98 ± 2.44	35.22 ± 2.47	0.15
Weight At Injection (kg)	2.29 ± 0.63	2.18 ± 0.91	0.50

BSID Patients Identified For Analysis

Ten patients who received low-dose IVB and 13 patients who received high-dose IVB completed a BSID test. Four patients were excluded from the analysis because they received IVB doses significantly higher or lower than those set for the high- and low-dose IVB cohorts. Two patients were excluded for receiving injections on two different dates. Of the 10 low-dose IVB patients, 8 patients received 0.0125mL IVB OU, 1 patient received 0.025mL OD, and 1 patient received 0.015mL IVB OU. In the high-dose IVB cohort, all 13 patients received 0.025mL IVB OU. The four patients who were excluded received a total IVB dosage of 0.08mL or 0.0125mL. Patient cohort breakdowns from the initial 89-patient count to the final patients who met criteria for analysis are summarized per BINS/BSID test status and IVB dosage in Fig. 1.

Low and High Dose BSID Cohort Data

The low-dose average BSID scores were 62.5 ± 12.96 CC, 63.7 ± 15.63 LC, 3.5 ± 2.84 LRe, 3.7 ± 2.41 LE, 61 ± 14.63 MC, 4 ± 2.91 FM, and 2.7 ± 2.67 GM. In the low-dose cohort, mean GA was 24.1 ± 1.37 weeks, BW 0.556 ± 0.097 kg, WAI 2.01 ± 0.52 kg, AAI 35.06 ± 2.37 weeks, and AT 24.1 ± 2.03 months. High-dose BSID average scores were 78.85 ± 18.61 for the CC standard score, 79.08 ± 19.67 for the LC standard score, 6.08 ± 2.96 for the LR communication scaled score, 6.69 ± 3.84 for the LE communication scaled score, 73.00 ± 19.90 for the MC standard score, 5.85 ± 3.76 for the FM scaled subscore, and 5.00 ± 3.14 for the GM scaled subscore. In the high-dose cohort, mean GA was 24.46 ± 1.20 weeks, BW 0.61 ± 0.13 kg, WAI 2.29 ± 0.67, AAI 36.38 ± 2.74 weeks, and AT 23.15 ± 1.77 months.

The high-dose BSID cohort had statistically significantly higher CC score ($p = 0.028$), LR score ($p = 0.047$), and LE communication score ($p = 0.043$). As expected, dosage per weight showed a statistically significantly greater value in the high-dose BSID group and all high-dose BINS groups as well. GA, BW, WAI, AAI, AT, and the remaining scores (LC standard [$p = 0.056$], MC standard [$p = 0.12$], FM scaled [$p = 0.21$], and GM scaled [$p = 0.077$]) showed no statistically significant difference between the two BSID cohorts. After Bonferroni correction, none of the BSID score differences between dose cohorts remained statistically significant (corrected p-values: CC = 0.20, LC = 0.39, LR = 0.33, LE = 0.30, MC = 0.84, FM = 1.00, GM = 0.54). Results were not statistically significant regarding risk severity distributions between the two groups for all categories. Fisher exact p-value results were 0.20 for CC, 0.65 for LC, 0.38 for LR, 0.64 for LE, 0.089 for MC, 0.20 for FM, and 0.16 for GM. Distributions of comorbidities assessed showed no statistically significant difference as well between the two dose groups. Data values of both dose cohorts are shown in Tables 3, 4, and 5.

Table 3
Comparison of Bayley Scales of Infant Development (BSID) Scores Between Low-Dose and High-Dose IVB Cohorts

Outcome Measured	Low Dose (n = 10)	High Dose (n = 13)	p-value	Bonferroni-corrected p-value
Cognitive Composition Score	62.50 ± 12.96	78.85 ± 18.61	0.028*	0.20
Language Composition Score	63.70 ± 15.63	79.08 ± 19.67	0.056	0.39
Receptive Communication Scaled Score	3.50 ± 2.84	6.08 ± 2.96	0.047*	0.33
Expressive Communication Scaled Score	3.70 ± 2.41	6.69 ± 3.84	0.043*	0.30
Motor Composition Score	61.00 ± 14.63	73.00 ± 19.90	0.12	0.84
Fine Motor Scaled Score	4.00 ± 2.91	5.85 ± 3.76	0.21	1.00
Gross Motor Scaled Score	2.70 ± 2.67	5.00 ± 3.14	0.077	0.54
Gestational Age (weeks)	24.10 ± 1.37	24.46 ± 1.20	0.51	-
Age at Injection (weeks)	35.06 ± 2.37	36.38 ± 2.74	0.22	-
Age at Test (months)	24.1 ± 2.025	23.15 ± 1.77	0.25	-
Birth Weight (kg)	0.556 ± 0.0973	0.61 ± 0.13	0.29	-
Weight 1st Injection (kg)	2.01 ± 0.52	2.29 ± 0.67	0.28	-
Dosage per infant weight (ml/kg)	0.0136 ± 0.00431	0.0234 ± 0.00675	0.00058*	-

Table 4
Fisher Exact Test Results for BSID Subcategory Risk Interpretations Between Low-Dose and High-Dose IVB Cohorts

BSID Subcategory	Fisher Exact Test p-value
Cognitive Composition	0.20
Language Composition	0.65
Receptive Communication	0.38
Expressive Communication	0.64
Motor Composition	0.089
Fine Motor	0.20
Gross Motor	0.16

Table 5
Fisher Exact Test Results for BSID Comorbidities Between Low-Dose and High-Dose IVB Cohorts

Comorbidity	Low Dose (n = 10)	High Dose (n = 13)	Fisher Exact Test p-value
Neurodevelopmental	9	11	1.0
Pulmonary	9	8	0.18
Psychiatric	1	3	0.60
Hearing Loss	4	1	0.13

Low and High Dose 3–4 Month BINS Subtest Cohort Data

Of the 40 patients who received a BINS test, 7 low-dose IVB patients received a 3–4 month subtest, and 7 high-dose IVB patients received a 3–4 month subtest. All high-dose BINS patients (3–4, 5–6, 7–10, and 11–15 months) received bilateral doses. In the low-dose cohort, all 7 patients received bilateral doses, and the average BINS scores with standard deviations were 5.87 ± 1.57 for total score, 2.86 ± 1.21 for neurological, 0.71 ± 0.76 for receptive communication, and 2.29 ± 0.49 for expressive communication. The 3–4 month subtest does not test for the cognitive component. Low-dose 3–4 month BINS mean GA was 23.7 ± 0.76 weeks, BW 0.64 ± 0.12 kg, WAI 2.238 ± 0.442, AAI 35.43 ± 1.13 weeks, and AT 6.85 ± 0.38 months. 4 patients had high-risk BINS interpretations. Three patients were at moderate risk, and zero patients were low risk. In the high-dose cohort, the average and standard deviation scores were 7.43 ± 1.13 for total score, 4.00 ± 0.82 for neurological score, 1.00 ± 0.00 for language receptive score, and 2.43 ± 0.53 for language expressive score. High dose 3–4 month BINS mean GA was 24.29 ± 1.38 weeks, BW 0.64 ± 0.13 kg, WAI 2.53 ± 0.73, AAI 37.04 ± 3.30 weeks, and AT 7.14 ± 0.38 months. GA, BW, WAI, AAI, AT, and all BINS subscores showed no statistically significant difference between the two BINS cohorts ($p > 0.05$). Risk interpretation distributions between both dosage groups revealed a p-value of 0.59 ($p > 0.05$). Comorbidity distributions were similar between the two 3–4 month BINS dose groups. Data values of both 3–4 month BINS dose cohorts are shown in Tables 6, 7, and 8.

Table 6
Comparison of 3 to 4 Month BINS Test Scores Between Low-Dose and High-Dose IVB Cohorts

Outcome Measured	Low Dose IVB (n = 7)	High Dose IVB (n = 7)	p-value
Total Score	5.87 ± 1.57	7.43 ± 1.13	0.053
Neurological	2.86 ± 1.21	4.0 ± 0.82	0.061
Receptive Communication	0.71 ± 0.76	1.0 ± 0.00	0.34
Expressive Communication	2.29 ± 0.49	2.43 ± 0.53	0.61
Cognitive	N/A	N/A	N/A
Gestational Age (weeks)	23.7 ± 0.76	24.29 ± 1.38	0.36
Age at Injection (weeks)	35.43 ± 1.13	37.04 ± 3.30	0.24
Age at Test (months)	6.85 ± 0.38	7.14 ± 0.38	0.18
Birth Weight (kg)	0.64 ± 0.12	0.64 ± 0.13	0.95
Weight 1st Injection	2.238 ± 0.442	2.53 ± 0.73	0.41
Dosage per infant weight (ml/kg)	0.012 ± 0.0025	0.021 ± 0.0062	0.0055

Table 7
BINS 3 to 4 Month Subtest Risk Interpretation Outcomes

Risk Interpretation (n)	Low Dose IVB	High Dose IVB	p-value
High Risk	4	2	
Moderate Risk	3	5	
Low Risk	0	0	
Fisher Exact Test Result	-	-	0.59

Table 8
Fisher Exact Test Results for 3 to 4 Month BINS Comorbidities Between Low-Dose and High-Dose IVB Cohorts

Comorbidity	Low Dose (n = 7)	High Dose (n = 7)	Fisher Exact Test p-value
Neurodevelopmental	5	6	1.0
Pulmonary	6	3	0.27
Psychiatric	0	2	0.46
Hearing Loss	2	0	0.46

Low and High Dose 5–6 Month BINS Subtest Cohort Data

Eight low-dose IVB and 9 high-dose IVB patients received a 5–6 month BINS subtest. In the low-dose cohort, 7 patients received bilateral doses, with 1 patient receiving a unilateral dose. Average scores were 5.38 ± 4.21 for total score, 1.88 ± 1.73 for neurological score, 0.38 ± 0.52 for language receptive score, 2 ± 1.41 for language expressive score, and 1.13 ± 1.25 for cognitive score. Low dose 5–6 month BINS mean GA was 24.13 ± 0.36 weeks, BW 0.62 ± 0.10 kg, WAI 1.99 ± 0.50 kg, AAI 34.95 ± 2.20 weeks, and AT 9 ± 2.33 months. Seven patients had a high-risk score interpretation, whereas only 0 and 1 patients had moderate and low score interpretations, respectively. In the high dose cohort, average scores were 7.89 ± 2.47 for total score, 2.67 ± 1.00 for neurological score, 0.33 ± 0.50 for language receptive score, 2.78 ± 0.97 for language expressive score, and 2.11 ± 0.78 for cognitive score. High dose 5–6 month BINS mean GA was 23.67 ± 0.71 weeks, BW 0.60 ± 0.11 kg, WAI 2.47 ± 0.72 kg, AAI 36.50 ± 3.18 weeks, and AT 8.11 ± 1.54 months. GA, BW, WAI, AAI, AT, and all BINS subscores showed no statistically significant difference between the two BINS cohorts ($p > 0.05$). Risk interpretation distributions compared between the two groups revealed a p-value of 0.21 ($p > 0.05$). Distributions of comorbidities assessed via Fisher's exact tests showed no statistically significant difference as well between the two 5–6 month BINS dose groups. Data values of both 5–6 month BINS dose cohorts are shown in Tables 9,10, and 11.

Table 9
Comparison of 5 to 6 Month BINS Test Scores Between Low-Dose and High-Dose IVB Cohorts

Outcome Measured	**Low Dose IVB (n = 8)**	**High Dose IVB (n = 9)**	**p-value**
Total Score	5.38 ± 4.21	7.89 ± 2.47	0.15
Neurological	1.88 ± 1.73	2.67 ± 1.00	0.26
Receptive Communication	0.38 ± 0.52	0.33 ± 0.50	0.87
Expressive Communication	2 ± 1.41	2.78 ± 0.97	0.20
Cognitive	1.13 ± 1.25	2.11 ± 0.78	0.066
Gestational Age (weeks)	24.13 ± 0.36	23.67 ± 0.71	0.12
Age At Injection (weeks)	34.95 ± 2.20	36.50 ± 3.18	0.27
Age at Test (months)	9 ± 2.33	8.11 ± 1.54	0.36
Birth Weight (kg)	0.62 ± 0.10	0.60 ± 0.11	0.68
Weight 1st Injection	1.99 ± 0.50	2.47 ± 0.72	0.16
Dosage per infant weight (ml/kg)	0.0135 ± 0.0048	0.022 ± 0.0064	0.013*

Table 10
BINS 5 to 6 Month Subtest Risk Interpretation Outcomes

Risk Interpretation (n)	Low Dose IVB (n = 8)	High Dose IVB (n = 9)	p-value
High Risk	7	6	
Moderate Risk	0	3	
Low Risk	1	0	
Fisher Exact Test Result	-	-	0.21

Table 11
Fisher Exact Test Results for 5 to 6 Month BINS Comorbidities Between Low-Dose and High-Dose IVB Cohorts

Comorbidity	Low Dose (n = 8)	High Dose (n = 9)	Fisher's exact test p-value
Neurodevelopmental	6	8	0.58
Pulmonary	7	4	0.13
Psychiatric	0	3	0.21
Hearing Loss	1	0	0.47

Low and High Dose 7–10 Month BINS Subtest Cohort Data

Eight low-dose IVB patients and 4 high-dose IVB patients completed a 7-10-month BINS subtest. In the low-dose cohort, 7 patients received bilateral doses, with 1 patient receiving a unilateral dose. Average scores were 5.75 ± 4.10 for total score, 1.75 ± 1.04 for neurological score, 0.25 ± 0.46 for language receptive score, 1.5 ± 1.51 for language expressive score, and 1.63 ± 0.92 for cognitive score. Low dose 7–10 month BINS mean GA was 24.50 ± 1.31 weeks, BW 0.56 ± 0.093 kg, WAI 1.87 ± 0.43 kg, AAI 35.6 ± 2.31 weeks, and AT 10.88 ± 3.27 months. Seven patients had a high-risk score interpretation, whereas only one and zero had moderate and low risk score interpretations, respectively. In the high dose cohort, average scores were 3.5 ± 4.36 for total score, 1.5 ± 0.58 for neurological score, 0.25 ± 0.5 for language receptive score, 1.0 ± 2.0 for language expressive score, and 0.75 ± 1.5 for cognitive score. Three patients had a high-risk score interpretation, whereas only one and zero patients had moderate and low risk interpretations, respectively. High dose 7–10 month BINS mean GA was 24.0 ± 0 weeks, BW 0.59 ± 0.13 kg, WAI 2.12 ± 0.75 kg, AAI 35.28 ± 3.48 weeks, and AT 11.5 ± 5.51 months. GA, BW, WAI, AAI, AT, and all BINS subscores showed no statistically significant difference between the two BINS cohorts ($p > 0.05$). Risk interpretation distributions compared between the two groups revealed a p-value of 0.999 ($p > 0.05$). Distributions of comorbidities showed no statistically significant difference as well between the two 7–10 month BINS dose groups. Data values of both 7–10 month BINS dose cohorts are shown in Tables 12,13, and 14.

Table 12
Comparison of 7 to 10 Month BINS Test Scores Between Low-Dose and High-Dose IVB Cohorts

Outcome Measured	Low Dose IVB (n = 8)	High Dose IVB (n = 4)	p-value
Total Score	5.75 ± 4.10	3.5 ± 4.36	0.40
Neurological	1.75 ± 1.04	1.5 ± 0.58	0.67
Receptive Communication	0.25 ± 0.46	0.25 ± 0.5	1.0
Expressive Communication	1.5 ± 1.51	1.0 ± 2.0	0.64
Cognitive	1.63 ± 0.92	0.75 ± 1.5	0.23
Gestational Age (weeks)	24.50 ± 1.31	24.0 ± 0	0.47
Age At Injection (weeks)	35.6 ± 2.31	35.28 ± 3.48	0.96
Age at Test (months)	10.88 ± 3.27	11.5 ± 5.51	0.81
Birth Weight (kg)	0.56 ± 0.093	0.59 ± 0.13	0.62
Weight 1st Injection	1.87 ± 0.43	2.12 ± 0.75	0.48
Dosage per infant weight (ml/kg)	0.015 ± 0.0045	0.0259 ± 0.0094	0.023*

Table 13
BINS 7 to 10 Month Subtest Risk Interpretation Outcomes

Risk Interpretation (n)	Low Dose IVB (n = 8)	High Dose IVB (n = 4)	p-value
High Risk	7	3	
Moderate Risk	1	1	
Low Risk	0	0	
Fisher Exact Test Result	-	-	0.999

Table 14
Fisher Exact Test Results for 7 to 10 Month BINS Comorbidities Between Low-Dose and High-Dose IVB Cohorts

Comorbidity	Low Dose (n = 8)	High Dose (n = 4)	Fisher Exact Test p-value
Neurodevelopmental	8	4	1.0
Pulmonary	6	4	0.515
Psychiatric	1	1	1.0
Hearing Loss	1	1	1.0

Low and High Dose 11–15 Month BINS Subtest Cohort Data

Ten low-dose IVB patients and three high-dose IVB patients completed an 11-15-month BINS subtest. In the low-dose cohort, 9 patients received bilateral doses, with 1 patient receiving a unilateral dose. Average scores were 3.3 ± 2.87 total, 1.1 ± 1.29 neurological, 0.9 ± 0.88 language receptive, 0.7 ± 0.82 language expressive, and 0.6 ± 1.07 cognitive. Low dose 11–15 month BINS mean GA was 23.70 ± 0.48 weeks, BW 0.63 ± 0.096 kg, WAI 2.02 ± 0.57 kg, AAI 34.42 ± 1.90 weeks, and AT 9.4 ± 2.27 months. Eight patients had a high-risk interpretation, whereas only 2 and 0 had a moderate and low-risk interpretation. In the high dose cohort, average scores were 5.33 ± 4.04 for total score, 1.33 ± 0.47 for neurological score, 1.33 ± 0.47 for language receptive score, 1.0 ± 1.0 for language expressive score, and 1.67 ± 1.53 for cognitive score. High dose 11–15 month BINS mean GA was 23.67 ± 0.58 weeks, BW 0.60 ± 0.14 kg, WAI 1.81 ± 0.66 kg, AAI 33.50 ± 2.85 weeks, and AT 10.67 ± 3.51 months. Two patients had a high-risk score interpretation, whereas only 1 and 0 had a moderate and low-risk score interpretation. T-test results for average BINS scores were 0.34 for total score, 0.78 for neurological score, 0.44 for language receptive score, 0.61 for language expressive score, and 0.19 for cognitive score ($p > 0.05$). GA, BW, WAI, AAI, AT, and all BINS subscores showed no statistically significant difference between the two BINS cohorts ($p > 0.05$). The Fisher exact test result comparing risk distributions was 1.00 ($p > 0.05$). Distributions of comorbidities showed no statistically significant difference as well between the two 11–15 month BINS dose groups. Data values of both 11–15 month BINS dose cohorts are shown in Tables 15, 16, and 17.

Table 15
Comparison of 11 to 15 Month BINS Test Scores Between Low-Dose and High-Dose IVB Cohorts

Outcome Measured	Low Dose IVB (n = 10)	High Dose IVB (n = 3)	p-value
Total Score	3.3 ± 2.87	5.33 ± 4.04	0.34
Neurological	1.1 ± 1.29	1.33 ± 0.47	0.78
Receptive Communication	0.9 ± 0.88	1.33 ± 0.47	0.44
Expressive Communication	0.7 ± 0.82	1.0 ± 1.0	0.61
Cognitive	0.6 ± 1.07	1.67 ± 1.53	0.19
Gestational Age (weeks)	23.70 ± 0.48	23.67 ± 0.58	0.92
Age at Injection (weeks)	34.42 ± 1.90	33.50 ± 2.85	0.52
Age at Test (months)	9.4 ± 2.27	10.67 ± 3.51	0.46
Birth Weight (kg)	0.63 ± 0.096	0.60 ± 0.14	0.72
Weight 1st Injection (kg)	2.02 ± 0.57	1.81 ± 0.66	0.61
Dosage per infant weight (ml/kg)	0.014 ± 0.0046	0.0299 ± 0.0097	0.0023*

Table 16
BINS 11 to 15 Month Subtest Risk Interpretation Outcomes

Risk Interpretation (n)	Low Dose IVB (n = 10)	High Dose IVB (n = 3)	p-value
High Risk	8	2	
Moderate Risk	2	1	
Low Risk	0	0	
Fisher Exact Test Result	-	-	1.0

Table 17
Fisher Exact Test Results for 11 to 15 Month BINS Comorbidities Between Low-Dose and High-Dose IVB Cohorts

Comorbidity	Low Dose (n = 10)	High Dose (n = 3)	Fisher Exact Test p-value
Neurodevelopmental	8	3	1.00
Pulmonary	8	2	1.00
Psychiatric	0	0	1.00
Hearing Loss	3	0	0.528

Discussion

In this retrospective cohort study, we evaluated the association between two dosages of IVB and neurodevelopmental outcomes in premature infants with ROP, using BSID and BINS scores. Comparing BSID and BINS scores between the two dosage cohorts revealed a similar trend in results. Overall, in unadjusted comparisons, no statistically significant differences in neurodevelopmental outcomes were observed between the two dose cohorts after Bonferroni correction for multiple BSID subscore comparisons. Patients in the high-dose IVB group demonstrated greater BSID scores in the CC, LR, and LE communication domains. However, none of these differences remained statistically significant after Bonferroni correction for multiple comparisons. Hence, the greater neurodevelopmental scores observed in the high-dose IVB groups may reflect inherent differences between the groups rather than a true, dose-dependent effect.

Prior literature demonstrates mixed results regarding the neurodevelopmental safety of anti-VEGF therapy in ROP.[7,8,10,15,16] The use of lower IVB doses is a relatively new development, only widely adopted after the landmark 2017 PEDIG ROP1 study demonstrated the efficacy of a 0.004 mg dose (less than 1% of the original 0.625 mg dose).[12] As such, to our knowledge, only one study has investigated dose-dependent associations with neurodevelopmental outcomes, finding no correlation between dosage of IVB and BSID scores at 2 years.[13] Our results contribute to this evidence by suggesting that lower dosages do not necessarily translate into improved early neurodevelopmental outcomes, although causality cannot be established from our data. This study is also, to our knowledge, the first of its kind to

assess neurodevelopmental outcomes of ROP infants treated with IVB across a wide infant age range by incorporating both BINS and BSID results.

Several limitations should be considered when interpreting these findings. The relatively small sample size in the BSID and BINS groups (23 in the BSID cohort, 12–17 in the BINS cohorts) reduced statistical power. A multivariable logistic regression to simultaneously adjust for potential confounders (GA, BW, etc.) and their association with categorical risk-severity outcomes was considered but not performed, given the limited sample size in this study (n = 23 in the BSID cohort; n = 12–17 across the BINS age-stratified subtests). With this few subjects relative to the number of candidate covariates, the ratio of covariates to subjects would have been insufficient to produce stable, reliable regression estimates. Measured cohort characteristics via univariate analyses were similar between groups; however, residual confounding cannot be fully excluded without a larger sample. Moreover, according to the BINS test protocol, infants unable to complete age-appropriate subtests were subsequently administered lower age-range subtests. While this minimized missing data, it may have inflated BINS scores and affected score interpretation. Thus, the BINS data may represent overestimated scores. Furthermore, as dosages assessed were limited to dosages administered according to practice guidelines over time, only two dosages of IVB were assessed, so our population may not represent all patients with ROP undergoing IVB treatment. Despite our best efforts to descriptively account for measured developmental factors, the variability among patients may not have been fully captured. Differences in socioeconomic factors, duration of supplemental oxygen administration, and oxygen saturation maintenance levels in the NICU may have influenced neurodevelopmental outcomes independently of IVB dosage.[17,18]

In conclusion, given the many factors that contribute to poor neurodevelopment in a preterm infant, this study demonstrates that isolating factors, such as IVB dosage, that may contribute to poor neurodevelopment in preterm ROP infants remains a challenge. Nonetheless, in this small retrospective cohort, unadjusted analyses found no evidence that lower IVB dosage was associated with improved neurodevelopmental outcomes in preterm infants with ROP. Our results suggest that confounding factors relating to prematurity itself may have a greater influence on neurodevelopment than IVB dose alone. Larger, prospective studies with additional standardized dosing and extended follow-up that control for additional factors, such as socioeconomic status and NICU oxygenation status, are needed to determine the neurodevelopmental safety of IVB in this vulnerable patient population.

Declarations

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Competing Interests: The authors have none to disclose.

Author Contributions: TK contributed to investigation, data curation, formal analysis, and writing – original draft and review & editing. ST contributed to conceptualization, formal analysis, and writing – review & editing. MYZ contributed to writing – original draft and review & editing. CB contributed to

writing – original draft and review & editing. MGH contributed to writing – original draft and review & editing. KB contributed to writing – original draft and review & editing. FO contributed to supervision and writing – review. EH contributed to supervision, conceptualization, formal analysis, and writing – review & editing.

Ethics: This study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Akron Children's Hospital (IRB approval number: 2024-131). Given the retrospective nature of the study and use of de-identified data obtained through electronic health record review, the requirement for individual informed consent was waived by the IRB. All patient data were handled in compliance with HIPAA regulations to protect patient confidentiality.

Availability of Data and Materials: The dataset analyzed in this study is not publicly available due patient privacy considerations.

Consent For Publication: Not Applicable. This manuscript does not contain any form of identifiable data of any individual.

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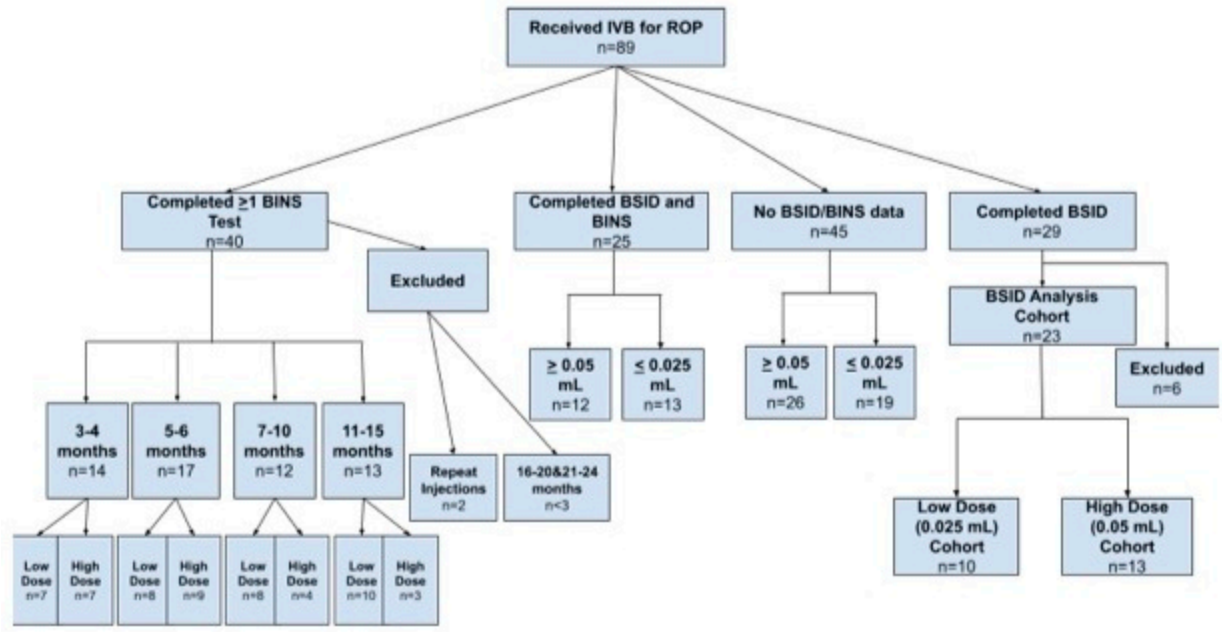
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Figures

Figure 1. BSID and BINS Patient Cohort Flow Chart Diagram



Note: BINS Subtests total 56 visits across 40 patients; some infants were tested at multiple ages.

Figure 1

BSID and BINS Patient Cohort Flow Chart Diagram. Flow diagram summarizing patient cohort breakdowns from the initial 89 infants who received intravitreal bevacizumab (IVB) for retinopathy of prematurity (ROP), through BSID and/or BINS test completion status, dosage cohort assignment (>0.05 mL and < 0.025 mL), and age-stratified BINS subtest groupings to the final low (0.025 mL) and high dose (0.05 mL) BSID analysis cohorts.