ORIGINAL RESEARCH

Postnatal Growth Trajectories and Neurodevelopmental Outcomes Following Bevacizumab Treatment for Retinopathy of Prematurity

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Purpose: To investigate the postnatal growth and neurodevelopment of infants with retinopathy of prematurity (ROP) treated with intravitreal bevacizumab (IVB).

Patients and Methods: This was a retrospective comparative study. A total of 262 infants were divided among three study groups: 22 treated with intravitreal bevacizumab, 55 treated with laser, and 185 with ROP that resolved without treatment. Infants with nonviable course or hydrocephalus, a source of non-physiologic weight gain, were excluded. Neurodevelopment was assessed with Bayley III scores at 17–28 months if available and presence of hearing loss or cerebral palsy. Weekly weight, height, and head circumference from birth through 50 weeks postmenstrual age (PMA) were modeled to determine differences in growth trajectories following treatment.

Results: Comparison of postnatal growth curves from the time of treatment to 50 weeks PMA showed no significant differences in growth trajectories between groups after adjusting for the corresponding growth parameters at birth. Comparison of Bayley scores in patients with available data (n = 120) showed no significant differences. There was an increased risk of cerebral palsy in the IVB group after logistic regression adjusting for baseline confounders, but this did not retain statistical significance after applying the false discovery rate correction for multiple testing.

Conclusion: To our knowledge, this is the first large retrospective study to examine longitudinal growth in infants treated with IVB compared to controls. There were no significant differences in postnatal growth or neurodevelopmental outcomes between groups, which overall continue to support the safety of bevacizumab treatment for ROP.

Keywords: pediatric retina, ROP, laser, bevacizumab, neurodevelopment, growth

Introduction

Retinopathy of prematurity (ROP) is a leading cause of childhood blindness characterized by neovascularization of the immature retina that can progressively lead to retinal detachment. The pathogenesis of ROP is thought to involve two phases, a hyperoxic phase followed by a hypoxic phase.[1] In phase one, excess oxygen exposure due to the extrauterine environment or supplemental oxygen causes downregulation of growth factors and termination of retinal blood vessel growth. During this phase, vascular endothelial growth factor (VEGF), an essential factor in angiogenesis, is suppressed. In phase two, increasing metabolic demands of the maturing retina cause hypoxic ischemia, upregulated VEGF, and subsequent vasoproliferation.

The current most widely accepted treatment for ROP is peripheral laser ablation, which has shown to improve visual, structural, and refractive outcomes.[2] However, laser photocoagulation is destructive to the retina, and more recent studies

on the use of anti-VEGF agents have shown that intravitreal bevacizumab (IVB) monotherapy is an effective treatment for ROP.[3] The use of IVB as a primary treatment has quickly gained popularity because it does not require general anesthesia, is more easily tolerated by sicker babies, and allows further development of peripheral retinal vessels before possible laser treatment is needed.

However, due to the anti-angiogenic effects of anti-VEGF agents, concern has risen regarding the systemic effects of IVB injection in premature infants.[4] The presence of bevacizumab in the systemic circulation after intravitreal injection has been observed for as long as 8 weeks after injection, while serum levels of VEGF were suppressed for the same duration.[5]

Systemic VEGF plays a key role in organogenesis and neural tube development[6,7] and may have a neuroprotective effect during periods of hypoxic cerebral injury, the most common known cause of cerebral palsy.[8] VEGF-mediated angiogenesis has also been shown to affect adipose tissue growth and function, contributing to weight gain and insulin resistance.[9] Furthermore, the interplay between VEGF and IGF-1 has prompted interest in postnatal growth rate as a prognostic factor in developing ROP.[10–13] The potential consequences of anti-VEGF therapy on these physiological processes are not completely understood. The goal of this study is to investigate the postnatal growth and neurodevelopment of preterm infants treated with IVB for ROP.

Patients and Methods

Subjects and Grouping

This study was approved by the institutional review boards of Ann & Robert H. Lurie Children's Hospital of Chicago and Northwestern University in Chicago, Illinois. All procedures adhered to the tenets of the Declaration of Helsinki.

All the patients screened for ROP at Ann & Robert H. Lurie Children's Hospital of Chicago and Prentice Women's Hospital from 2008 to 2019 were identified. Inclusion criteria included infants with ROP that resolved without treatment (group 0), infants with ROP treated with laser photocoagulation (group 1), and infants with ROP treated with initial bevacizumab monotherapy (group 2). Indications for treatment were type I ROP as defined by the Early Treatment for Retinopathy of Prematurity study.[2] Infants with nonviable course, infants who were transferred or lost to follow up before growth and neurodevelopment could be measured, and infants with hydrocephalus, which is a source of non-physiologic weight gain, were excluded. Baseline characteristics, hospital course, and systemic comorbidities were recorded and compared between groups.

Neurodevelopmental Outcomes Assessment

In patients with sufficient follow-up and available data, the Bayley Scales of Infant and Toddler Development-III scores at 17–28 months of age were used as a representation of neurodevelopmental outcomes. Poor neurodevelopmental outcomes were defined as Bayley III composite scores <85 in cognitive, language, or motor domains. Severe neurodevelopmental impairment was defined as a Bayley III composite score <70 in any domain. The presence or absence of hearing loss or cerebral palsy at the latest follow-up was also recorded and compared between groups as a separate proxy for neurodevelopmental outcomes.

Growth Outcomes Assessment

Weekly weight, height, and head circumference measurements from birth through 50 weeks postmenstrual age (PMA) were recorded, statistically modeled, and compared between groups to examine changes in growth trajectory over time. The mean weight, height, and head circumferences of each treatment group were also plotted against a standard, the Fenton preterm growth chart, to qualitatively examine growth trends over time by gender.

Statistical Analysis

Statistical analysis was performed using R software version 4.1.0 within RStudio version 1.4.1717 (R Core Team, Vienna, Austria). P-values were adjusted using the Benjamini–Hochberg procedure to control the false discovery rate (adjusted q < 0.05 for statistical significance) for the neurodevelopmental outcome assessment.

Demographic characteristics, baseline clinical data, and neurodevelopmental outcomes were expressed as frequency and percentage for categorical variables, and median and interquartile ranges (IQR) for continuous variables due to skewed distributions. Statistical significance (unadjusted p < 0.05) and clinical importance were used to identify clinical characteristics as potential confounders. Differences across treatment types were assessed using Pearson's chi-squared or Fisher's exact test for categorical variables such as hearing loss, and Kruskal–Wallis test for continuous measures including Bayley scores. We used logistic regression to examine differences in cerebral palsy outcome by treatment type, adjusting for birth weight, gestational age, presence of intraventricular hemorrhage (IVH), and Apgar score at 5 minutes.

Mixed-effects modeling was used to examine changes in weight, height, and head circumference beginning from the earliest time of treatment. To model the non-linear relationship of time with height and head circumference, we introduced a quadratic term for time. The models of weight, height, and head circumference included a time-by-treatment-type interaction to assess differences in the changes in growth measures over time across treatment groups. The models were adjusted for initial birth weight, height, and head circumference, respectively.

Results
Patient Characteristics

A total of 262 patients (144 males and 118 females) were included in the final analysis. A flowchart showing inclusion and exclusion of patients is shown in Figure 1. Among these patients, 185 had ROP that resolved without treatment (Group 0), 55 had ROP treated with laser (Group 1), and 22 had ROP treated with bevacizumab (Group 2). Median PMA at treatment was 36.3 weeks in the bevacizumab group (IQR 35.3–38.1) and 38.3 weeks in the laser group (IQR 35.1–41.6); there was no statistically significant difference in the time of treatment using the Mann–Whitney U-test (p = 0.06).

Table 1 shows the demographics and baseline comorbidities of each group. The IVB group had younger median gestational age (24.9 weeks, IQR 24.0–25.9) than the laser group (25.1 weeks, IQR 24.5–25.3) and untreated group (26.1 weeks, IQR 25.3–28.0). The IVB group also had lower birth weight (672.5 g, IQR 547.5–771.2) compared to the laser
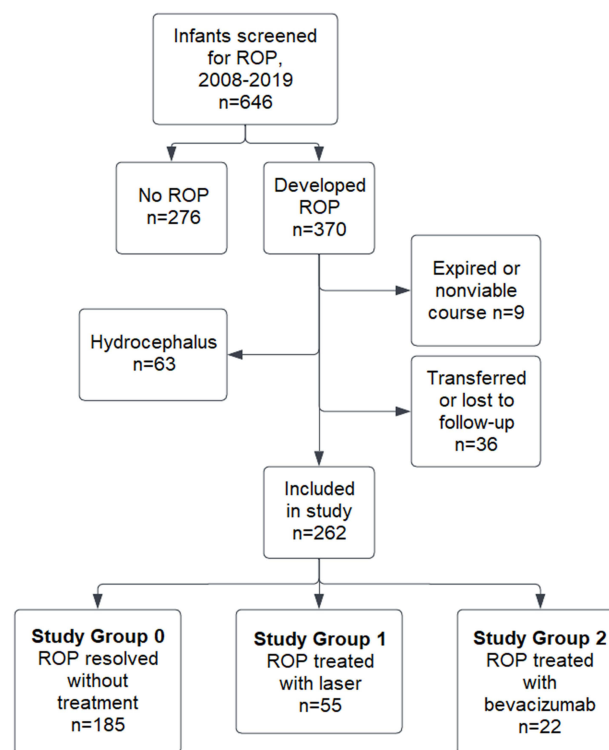
Figure 1 Flowchart showing inclusion and exclusion of patients during the study period.

Table 1 Baseline Demographics and Systemic Risk Factors of All Included Study Participants

Baseline Characteristics	No Treatment, N = 185	Laser, N = 55	IVB, N = 22	p-value[a]	q-value[b]
Sex, no. (%)				0.11	0.59
Male	95 (51%)	33 (60%)	16 (73%)		
Female	90 (49%)	22 (40%)	6 (27%)		
Gestational age (weeks), median (IQR)	26.1 (25.3, 28.0)	25.1 (24.5, 25.3)	24.9 (24.0, 25.9)	**<0.001**	**<0.001**
Birth weight (g), median (IQR)	870.0 (720.0, 1080.0)	740.0 (642.5, 825.0)	672.5 (547.5, 771.2)	**<0.001**	**<0.001**
Apgar 1 minute, median (IQR)	5 (2, 6)	3 (2, 5)	3 (1, 5)	0.056	0.41
Apgar 5 minutes, median (IQR)	7 (5.5, 8)	6 (5, 8)	6 (4, 7)	**0.042**	0.39
Small for gestation age, no. (%)	15 (8%)	1 (2%)	2 (9%)	0.19	0.67
Cesarean birth, no. (%)	112 (61%)	34 (63%)	15 (68%)	0.77	>0.99
Multiple birth, no. (%)	51 (28%)	17 (31%)	5 (23%)	0.72	>0.99
Antenatal steroid use, no. (%)	103 (56%)	38 (70%)	16 (73%)	0.069	0.41
Postnatal steroid use, no. (%)	86 (46%)	31 (56%)	16 (73%)	**0.043**	0.39
Necrotizing enterocolitis, no. (%)	59 (32%)	15 (27%)	8 (36%)	0.70	>0.99
PDA ligation, no. (%)	40 (22%)	15 (27%)	4 (18%)	0.60	>0.99
IVH grade 1 or 2, no. (%)	63 (34%)	18 (33%)	3 (14%)	0.15	0.67
IVH grade 3 or 4, no. (%)	18 (10%)	6 (11%)	2 (9%)	0.94	>0.99
Sepsis, no. (%)	49 (26%)	16 (30%)	10 (45%)	0.18	0.67
PVL, no. (%)	16 (9%)	4 (7%)	3 (14%)	0.62	>0.99
BPD, no. (%)	146 (79%)	40 (74%)	18 (82%)	0.73	>0.99
RDS, no. (%)	172 (93%)	49 (91%)	20 (91%)	0.68	>0.99

Notes: Statistically significant p-values are bolded. [a]Categorical variables were assessed using Pearson's Chi-squared test or Fisher's exact test, when applicable. Continuous variables were assessed using Kruskal–Wallis test. [b]False discovery rate correction for multiple testing.
Abbreviations: IVB, intravitreal bevacizumab; IQR, interquartile range; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; BPD, bronchopulmonary dysplasia; RDS, respiratory distress syndrome.

group (740.0 g, IQR 642.5–825.0) and untreated group (870.0 g, IQR 720.0–1080.0). Additionally, postnatal steroid use was higher in the IVB group (16/22, 73%) compared to laser (31/55, 56%) and untreated (86/185, 46%) groups. Finally, Apgar score at 5 minutes was found to be different between groups, with a median score of 6 in the IVB group (IQR 4–7), 6 in the laser group (IQR 5–8), and 7 in the untreated group (IQR 5.5–8).

Neurodevelopmental Outcomes

A total of 120 patients had available Bayley scores in the 17–28-month range: 12 treated with IVB, 31 treated with laser, and 77 without treatment. Baseline characteristics of this subset of patients are described in Table 2. Comparison of the Bayley III composite scores (Table 3) using the Kruskal–Wallis test with false discovery rate correction showed no significant differences in cognitive, language, or motor domains (q-value >0.99). Similarly, the frequency of poor neurodevelopmental outcomes, defined as a Bayley III score <85, was not significantly different across the groups in cognitive, language, or motor domains (q > 0.99). Finally, there were no differences in severe neurodevelopmental impairment, defined as any Bayley III score <70 (q >0.99).

The presence of hearing loss and cerebral palsy were also compared between groups (Table 4). There was no significant difference in the presence of hearing loss between groups (q > 0.99). Notably, the presence of cerebral palsy was significantly higher in the group treated with IVB (unadjusted p = 0.015); this statistical significance was retained after logistic regression adjusting for BW, GA, IVH, postnatal steroid use, and Apgar score at 5 minutes (OR 3.67, 95% CI 1.01–12.9, p = 0.043). However, after applying the false discovery rate correction for multiple testing, this finding failed to achieve significance (q > 0.99).

Postnatal Growth Outcomes

Figure 2 shows comparisons of weight, height, and head circumference trajectories following treatment with laser or bevacizumab. Individual growth measurements each week from birth through 50 weeks PMA were graphed on a scatter plot

Table 2 Baseline Demographics and Systemic Risk Factors for Participants with Bayley Scores

Baseline Characteristics	No Treatment, N = 77	Laser, N = 31	IVB, N = 12	p-value[a]	q-value[b]
Sex, no. (%)				0.27	0.56
Male	40 (52%)	19 (61%)	9 (75%)		
Female	37 (48%)	12 (39%)	3 (25%)		
Gestational age (weeks), median (IQR)	26.0 (25.3, 27.6)	24.4 (24.0, 26.2)	25.1 (24.5, 25.8)	**<0.001**	**0.014**
Birth weight (g), median (IQR)	847.0 (710.0, 1030.0)	735.0 (680.0, 790.5)	715.0 (577.5, 832.5)	**0.002**	**0.022**
Apgar 1 minute, median (IQR)	4 (2, 6)	2 (2, 4)	3 (1, 5)	**0.041**	0.26
Apgar 5 minutes, median (IQR)	7 (5, 8)	5.5 (4, 8)	6 (4, 7)	0.15	0.48
Small for gestation age, no. (%)	8 (10%)	0 (0%)	1 (8%)	0.18	0.48
Cesarean birth, no. (%)	51 (66%)	16 (52%)	7 (58%)	0.45	0.72
Multiple birth, no. (%)	27 (35%)	6 (19%)	3 (25%)	0.29	0.57
Antenatal steroid use, no. (%)	44 (57%)	21 (68%)	9 (75%)	0.29	0.57
Postnatal steroid use, no. (%)	35 (45%)	18 (58%)	7 (58%)	0.41	0.71
Necrotizing enterocolitis, no. (%)	22 (29%)	9 (29%)	5 (42%)	0.65	>0.99
PDA ligation, no. (%)	15 (19%)	11 (35%)	2 (17%)	0.17	0.48
IVH grade 1 or 2, no. (%)	30 (39%)	11 (35%)	3 (25%)	0.64	>0.99
IVH grade 3 or 4, no. (%)	10 (13%)	5 (16%)	1 (8%)	0.79	>0.99
Sepsis, no. (%)	22 (29%)	9 (29%)	3 (25%)	0.95	>0.99
PVL, no. (%)	6 (8%)	1 (3%)	0 (0%)	0.45	0.72
BPD, no. (%)	66 (86%)	23 (74%)	8 (67%)	0.21	0.48
RDS, no. (%)	70 (91%)	27 (87%)	11 (92%)	0.98	>0.99

Notes: Statistically significant p-values are bolded. [a]Categorical variables were assessed using Pearson's Chi-squared test or Fisher's exact test, when applicable. Continuous variables were assessed using Kruskal–Wallis test. [b]False discovery rate correction for multiple testing.
Abbreviations: IVB, intravitreal bevacizumab; IQR, interquartile range; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; BPD, bronchopulmonary dysplasia; RDS, respiratory distress syndrome.

Table 3 Comparison of Neurodevelopmental Outcomes Across Treatment Type Based on Bayley III Scores Collected at 17–28 Months

| Bayley III Score Domains	No Treatment, N = 77	Laser, N = 31	IVB, N = 12	p-value[a]	q-value[b]
Cognitive composite score, median (IQR)	95.0 (85.0, 100.0)	90.0 (82.5, 100.0)	90.0 (87.5, 96.2)	0.75	>0.99
Language composite score, median (IQR)	83.0 (77.0, 93.2)	79.0 (71.0, 94.0)	71.0 (68.0, 82.5)	0.11	>0.99
Motor composite score, median (IQR)	89.5 (76.0, 97.0)	88.0 (79.0, 94.0)	85.0 (82.8, 94.8)	0.90	>0.99
Cognitive composite score <85, no. (%)	15 (19%)	7 (23%)	3 (25%)	0.83	>0.99
Language composite score <85, no. (%)	30 (41%)	17 (55%)	5 (45%)	0.38	>0.99
Motor composite score <85, no. (%)	14 (18%)	9 (30%)	3 (25%)	0.36	>0.99
Severe impairment score <70, no. (%)	14 (19%)	5 (16%)	5 (42%)	0.20	>0.99

Notes: [a]Categorical variables assessed using Fisher's exact test. Continuous variables assessed using Kruskal–Wallis rank sum test. [b]False discovery rate correction for multiple testing.

Table 4 Association of Other Neurodevelopmental Measures with Treatment Status

Neuro-Developmental Measures	No Treatment, N = 185	Laser, N = 55	IVB, N = 22	p-value[a]	Odds Ratio	95% CI	p-value[b]	q-value[c]
Hearing loss, no. (%)	30 (16%)	6 (11%)	5 (24%)	0.42	-	-	-	>0.99
Cerebral palsy, no. (%)	13 (7%)	6 (11%)	6 (27%)	**0.015**	3.67	1.01–12.9	**0.043**	>0.99

Notes: Statistically significant p-values are bolded. [a]Fisher's exact test. [b]Logistic regression adjusted for BW, GA, IVH, postnatal steroid use, and Apgar 5 mins. [c]False discovery rate correction for multiple testing.

and converted into prediction lines using mixed-effects models. The time period of interest began from the earliest age at bevacizumab or laser treatment, which was 32 weeks PMA. Comparison of growth rates prior to treatment showed no significant differences in weight, height, and head circumference.
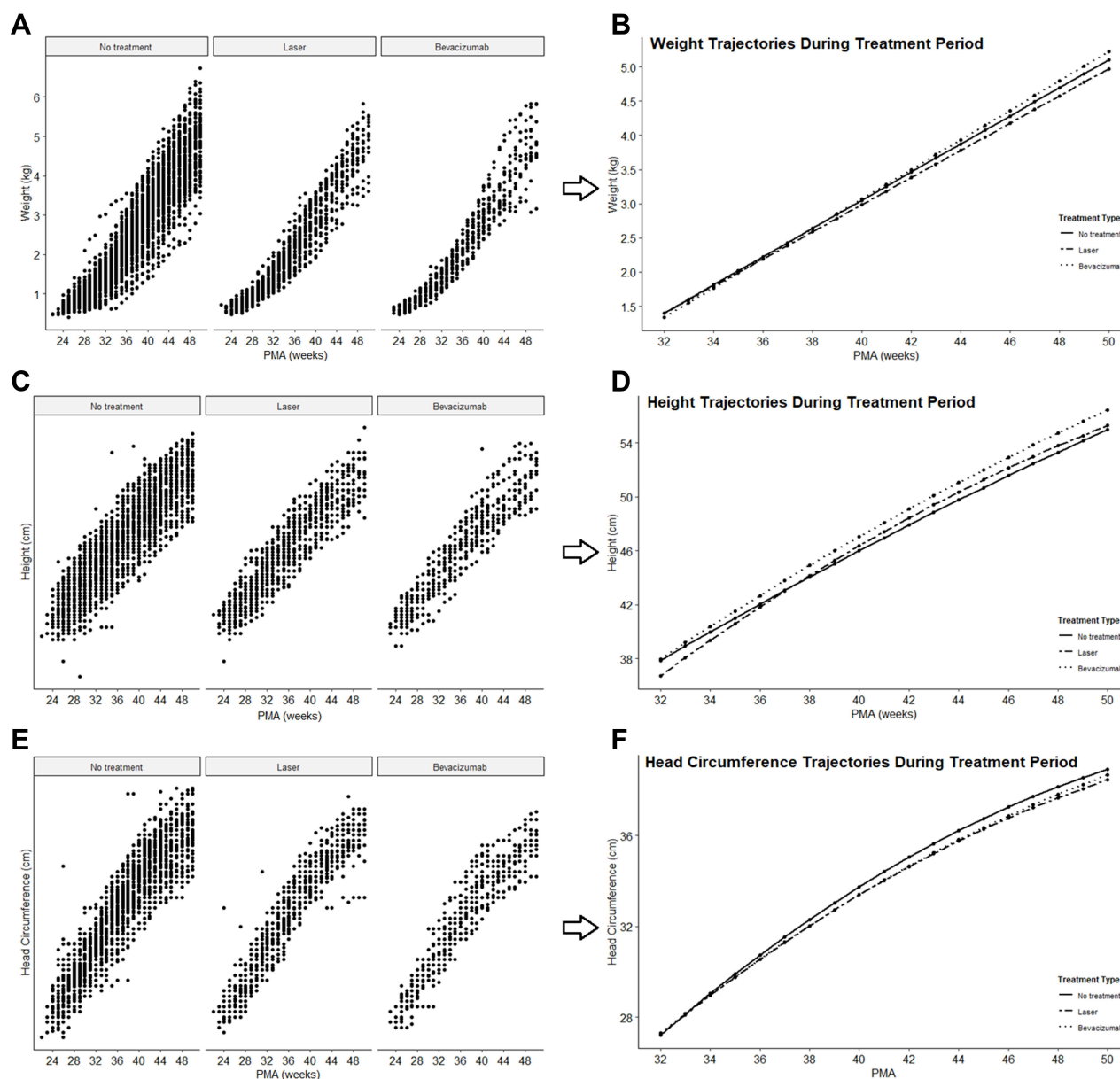
Figure 2 Postnatal growth trajectories during time period of ROP treatment and subsequent weeks of growth. Individual growth data from birth through 50 weeks PMA were plotted (**A**, **C** and **E**) and converted into prediction lines using mixed effects models (**B**, **D** and **F**). (**B**) Weight trajectories were not significantly different between groups after adjusting for initial birth weight. (**D**) Height trajectory for the bevacizumab group was not significantly different from the other study groups after adjusting for initial height at birth. Incidentally, the laser group showed a statistically different height trajectory compared to the untreated group. (**F**) Head circumference trajectories were not significantly different between groups after adjusting for initial head circumference at birth.

Comparison of weight trajectories after treatment, adjusted for initial birth weight, showed no significant difference in the bevacizumab group (p = 0.31) or the laser group (p = 0.38) compared to the untreated group. The proportion of variance explained by the model in total (fixed and random effects), R^2, was 98%. Comparison of height trajectories after treatment, adjusted for initial height at birth, showed no significant difference in the bevacizumab group compared to the untreated group (p = 0.42, R^2 = 95%). Incidentally, statistically significant differences were detected in the trajectory of the laser group compared to the untreated group (p = 0.01). Finally, comparison of head circumference trajectories, adjusted for initial head circumference at birth, showed no significant difference in growth across groups (bevacizumab vs untreated p = 0.23, laser vs untreated p = 0.44, R^2 = 96%).

Plotting of mean growth measures per week on the Fenton preterm growth chart qualitatively demonstrated percentile deterioration in weight, height, and head circumference from birth through 50 weeks PMA, regardless of sex or treatment status. At birth, mean weight in both sexes began around the 50th percentile range, then fell to the 10th percentile in males and 20th percentile in females. Mean height also began around the 50th percentile in both sexes, then fell to <3rd percentile in males and 3–10th percentile in females. Finally, mean head circumference at birth began around the 50th percentile and fell to 3–10th percentile in males; in females, head circumference deteriorated to 10th percentile over weeks 28–40 and recovered to the 30th percentile by 50 weeks PMA.

Discussion

The purpose of this study was to analyze postnatal growth and neurodevelopmental outcomes in a large single-center cohort of premature babies treated with IVB for ROP. To our knowledge, this is the first large retrospective study to compare longitudinal growth trends in infants treated with IVB to those who were treated with laser and untreated. The findings in this study were two-fold: our analysis of growth outcomes shows no difference in growth rates in weight, height, and head circumference over time in the IVB-treated group; in addition, we found no significant differences in Bayley III scores at 17–28 months between treatment groups.

Although VEGF has been shown to play a key role in neurodevelopment,[7] previous studies have largely found no detriment to neurodevelopmental outcomes in infants treated with IVB.[14–20] Bayley III scores have been the most commonly used metric to quantify neurodevelopment, and our analysis corroborates the majority of previous studies.

Several studies have found a higher risk of neurodevelopmental disability in infants treated with IVB,[21–23] but concerns with selection bias and baseline inequalities limit the generalizability of results.[24,25] A meta-analysis of eight studies conducted by Tsai et al showed no increased risk of severe neurodevelopmental impairment after IVB treatment, except for a minor difference in motor performance, the clinical effects of which are uncertain.[26] In contrast, another meta-analysis of thirteen studies conducted by Kaushal et al found significantly increased odds of cognitive impairment, defined by Bayley III score <85, associated with IVB.[27] Nevertheless, due to the low quality of evidence of studies used in both meta-analyses, there is consensus that further randomized control trials are needed to better understand systemic safety.

One additional concern of systemic IVB exposure is the potential risk of cerebral palsy, as suggested by Morin et al,[21] who found increased odds of composite severe neurodevelopmental disability (which included cerebral palsy) in infants treated with IVB. Several subsequent studies have investigated the frequency of cerebral palsy and have not found an association.[16,17,28] In our analysis, statistical analysis found an increased risk of cerebral palsy in the IVB group, even after adjusting for baseline confounders by logistic regression. However, this result was ultimately not statistically significant after false discovery rate correction, suggesting that this finding was likely a false-positive result in the setting of multiple testing.

It has been suggested that cerebral palsy is a movement disorder that is present from birth rather than a postnatal developmental disorder.[14] However, even in the absence of a genetic component, postnatal neurologic insults such as infection, trauma, sepsis, kernicterus, or hypoxia-ischemia can precipitate CP.[29] VEGF suppression could also theoretically fall into this category, as VEGF has been suggested to have a neuroprotective effect in hypoxic-ischemic brain injury.[8] Despite the high probability of a false-positive result in our study evidenced by the statistical correction, we ultimately could not fully exclude the possibility of cerebral palsy risk with IVB treatment, and further studies are needed to better understand their association.

Physical growth is another key measure of postnatal development, which is heavily influenced by VEGF activity.[6] In animal models, suppression of VEGF has shown context-dependent effects on insulin resistance and reduced weight gain, even with intravitreal injection.[9] In humans, Kong et al[30] measured weekly body weight gain from birth to 60 days in 24 infants treated with laser, 0.25 mg IVB, or 0.625 mg IVB. After adjusting for gestation age, sex, and birth weight, they found no significant differences in body weight at 60 days post treatment between groups. Due to the small sample size of that study, definite conclusions are limited but are consistent with the results of the present analysis.

Growth rate, the change in growth over time, is a more sensitive indicator of growth than a single measurement,[30] and absolute growth rate during the first year of life is not significantly different between the two sexes.[31] Comparison of

growth trajectories in the weeks prior to treatment showed similar growth rates between groups, supporting the consistent growth trends among all preterm infants in this retrospective study. There were additionally no overall differences in PMA at the time of treatment between the IVB and laser groups. It is possible that earlier or later individual ages at the time of treatment may affect the impact of IVB or laser on subsequent growth; however, the time of treatment is dictated by ROP severity, which can be confounded by risk factors that also affect postnatal growth.

Intravitreal bevacizumab can escape from the eye into the systemic circulation and has been detected within serum as early as one to two days after intravitreal injection, with correspondingly suppressed serum VEGF levels up to eight weeks after treatment.[5,30] Comparison of growth trends between treatment groups shows no significant differences in weight, height, or head circumference changes in the bevacizumab group compared to the laser and untreated groups up to 50 weeks PMA, which is up to 18 weeks after the earliest time of treatment in our sample. The incidental finding of height trajectory differences in the laser group compared to the untreated group may be due to the statistical growth model used; random variation within the data may cause a slightly different shape when fitting the prediction line and adding a quadratic term for time. Reassuringly, there was no significant difference between the IVB group and the laser group or the untreated group.

Additionally, comparison of mean growth measures to an established standard, the Fenton preterm growth chart, demonstrated deterioration in growth curve percentile regardless of sex and treatment status and is a known consequence of preterm birth.[31] Despite the potential of catch-up growth in these preterm infants, postnatal growth continues to lag behind their term counterparts, even into adolescence and adulthood. The significance of impaired growth has a variety of metabolic consequences and systemic complications such as hypertension and insulin resistance.[32] Overall, postnatal growth has been shown to be a prognostic factor associated with ROP and is an important consideration when investigating systemic outcomes; our results reassuringly did not find an impact of systemic bevacizumab exposure on these measures.

Limitations of this study include its retrospective nature; analysis of baseline characteristics and comorbidities has shown that, like previously published studies, infants treated with IVB have historically been smaller and sicker. These baseline differences can be adjusted for in statistical calculations but may not necessarily reflect real-life clinical consequences of using anti-VEGF agents in a vulnerable patient population. IVB treatment was generally for sicker children with anesthesia concerns or those with more posterior disease, and the choice of IVB versus laser treatment was not randomized due to the retrospective nature of this study. The proportion of patients with available Bayley scores was also higher in the IVB (55%) and laser (56%) groups compared to the untreated group (42%), which may have reflected selection bias for sicker patients that required more long-term follow-up. Despite this, there were no significant differences in Bayley scores between groups. Our limited sample size of IVB-treated patients may also limit the generalizability of neurodevelopmental findings, particularly our findings on cerebral palsy risk. Nevertheless, our robust comparison groups and novel analysis of growth outcomes provide additional data to the current literature surrounding systemic safety of IVB.

Conclusion

In all, anti-VEGF treatment for ROP has been shown to have comparable short-term efficacy to laser photocoagulation[3,33] and has increased in usage due to greater ease of administration, decreased destruction of the peripheral retina, and lower risk of myopia.[34] Studies on the systemic effects of these agents have been largely reassuring, but the lower quality of available evidence still warrants caution and investigation regarding their long-term effects on developing infants. Our results show no significant differences in postnatal growth, Bayley scores, hearing loss, and cerebral palsy compared to ROP infants receiving laser or no treatment. Further prospective, randomized studies will be needed to determine if anti-VEGF treatment for ROP indeed has clinically significant systemic consequences.

Ethics Statement

This study has obtained ethics approval from the institutional review boards of Ann & Robert H. Lurie Children's Hospital of Chicago and Northwestern University in Chicago, Illinois. Written informed consent was waived due to the

retrospective nature of the study, and the privacy of participants was ensured by anonymizing the data and securely storing all data in a private location.

Disclosure

The authors report no conflicts of interest in this work.

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