Bevacizumab for Retinopathy of Prematurity Is Not Associated With Systemic Hypertension

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ABSTRACT

Purpose: To evaluate for an association between systemic hypertension and intravitreal bevacizumab (IVB) for retinopathy of prematurity (ROP) treatment, due to a 2020 case report of a neonate with ROP developing systemic hypertension and posterior reversible encephalopathy syndrome (PRES) after IVB and limited data on long-term safety of IVB.

Methods: A retrospective cohort study was conducted using vital signs for 90 days, comparing IVB to laser treatment. The primary outcome was short-term hypertension, recorded for at least 3 consecutive days following treatment. As a secondary outcome, infants treated with IVB were also compared to infants with severe ROP who experienced spontaneous regression without treatment. Rates of long-term hypertension, based on chart diagnoses at discharge, were also reviewed. Neuroimaging was re-reviewed to evaluate for vasogenic edema consistent with PRES.

Results: Overall, 137 infants with severe ROP were included, of whom 94 required treatment. There were no baseline differences in neonatal comorbidities comparing laser to IVB. There was no difference on unadjusted or adjusted logistic regression comparing odds of short-term hypertension after IVB to laser (adjusted odds ratio: 0.69, 095% CI: 0.25, 1.87). There was no significant difference in the rate of long-term hypertension diagnoses by treatment group.

Conclusions: The lack of association between IVB and short-term systemic hypertension is reassuring. Further studies are warranted to confirm this.

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INTRODUCTION

Bevacizumab is an anti-vascular endothelial growth factor (VEGF) antibody commonly used off-label as intravitreal therapy for the treatment of adult diabetic retinopathy since the 2000s.[1-3] Although not yet approved for retinopathy of prematurity (ROP) treatment by the U.S. Food and Drug Administration, intravitreal bevacizumab (IVB) is widely used for the treatment of ROP primarily because of the Bevacizumab Eliminated the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) study in 2011. The BEAT-ROP was the first randomized control trial demonstrating the notably lower rate of disease recurrence in infants treated with IVB compared to laser therapy for posterior ROP, with superior structural and refractive outcomes also noted in the IVB group.[4,5]

Although the findings of the BEAT-ROP study were important in demonstrating IVB efficacy, the study did not assess the long-term safety of IVB in neonates.[5-7] Although most subsequent studies have

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focused on neurodevelopmental concerns,[8-14] a case report from 2020 published in *Pediatrics* described the first known case of a premature infant developing systemic hypertension 10 days after IVB treatment for stage 3 ROP.[15] Brain imaging was notable for cortical vasogenic edema and multifocal cortico-subcortical hemorrhages of the parieto-occipital region that improved after resolution of the hypertensive crisis. The patient's presentation was consistent with that of posterior reversible encephalopathy syndrome (PRES), a rare complication (< 0.5% incidence) of systemic bevacizumab.[16]

Although the relationship between bevacizumab and PRES is not well understood, the adult literature reports that the majority of PRES cases followed moderate or severe hypertensive crises.[17,18] PRES can be precipitated by other factors such as illness or chemotherapy medications, but because bevacizumab can cause hypertensive crises, the relationship may be worth further exploring.[16,17]

Subsequently, Twitty et al[19] reported a high rate of systemic hypertension within 30 days of treatment with IVB, although only 14% needed antihypertensive treatment. Because all patients in the aforementioned study received IVB treatment for ROP, the purpose of this study was to evaluate for an association between IVB and hypertension among infants with severe ROP, comparing those treated with IVB to those treated with laser or infants whose ROP spontaneously regressed.

PATIENTS AND METHODS

This study was a retrospective cohort study to evaluate an association between IVB treatment and subsequent systemic hypertension. Premature infants screened for ROP at The University of Chicago between January 2012 and April 2020 who developed type 1 ROP or type 2 ROP, as defined by the Early Treatment of ROP Study,[20] were included in this study. Infants with type 1 ROP were treated with either primary laser or primary IVB with delayed laser as described elsewhere.[21] All infants with type 2 ROP spontaneously regressed without treatment.

The primary outcome measure was the diagnosis of short-term hypertension, for 3 consecutive days as defined below, following treatment for ROP with IVB or laser. To determine if an infant developed hypertension, vital signs for patients were reviewed for 90 days after treatment, starting from the day of treatment for infants with type 1 ROP (IVB or laser). This time length of 90 days was chosen to be broad and encompass the 8 weeks that IVB remains in the systemic circulation after intravitreal injection, [22] although the case report described the incident at 10 days. Vital signs used were those recorded on nurses' flow sheets, with a median of five blood pressure readings per day. Oscillometric, noninvasive blood pressure measurements were used.

Other outcomes included odds of sustained hypertension comparing infants treated with IVB to infants treated with laser, as well as comparing infants treated with IVB to infants with type 2 ROP whose ROP resolved without treatment. For infants with type 2 ROP, vital signs were reviewed for 90 days, starting at 34 weeks' post-menstrual age (PMA).

Due to the high proportion of infants with short-term hypertension, the analysis was repeated, again reviewing vital signs for 10 days after treatment for type 1 ROP, based on the time frame of the case report.[15] Long-term outcomes were also reviewed, evaluating the proportion in infants in each treatment group who obtained a final chart diagnosis of hypertension.

Potential confounding factors were also explored, including: birth weight, gestational age, race/ethnicity, gender, bronchopulmonary dysplasia (typically defined as supplemental oxygen after 36 weeks), necrotizing enterocolitis (requiring surgery), severe intraventricular hemorrhage (grade 3 or grade 4), patent ductus arteriosus requiring surgical repair, history of umbilical arterial catheter placement, congenital or acquired renal disease, hypertension prior to treatment, and systemic neonatal steroid treatment (neonatal hydrocortisone, dexamethasone, and methylprednisolone).

Exclusion criteria for the primary and secondary outcomes included a lack of complete vital sign information. In collaboration with pediatric neonatology and neuroradiology, we also re-reviewed the available neuroimaging for the presence of vasogenic edema, which is indicative of PRES. Approval was obtained from the institutional review board at the University of Chicago (#IRB20-0685).

Short-term and Long-term Hypertension

Short-term hypertension was defined as more than 3 consecutive days with hypertension. Based on normative data among preterm infants, which varies based on PMA, hypertension for this study was de-

TABLE 1

PMA and Corresponding SBP and DBP Considered HTN

PMA (Weeks)	SBP/DBP
30, 31	> 80 / > 55
32, 33	> 83 / > 55
34, 35	> 85 / > 55
36, 37	> 87 / > 65
38, 39	> 92 / > 65
40, 41	> 95 / > 65
42, 43	> 98 / > 65
44	> 105 / > 68
> 44	> 110 / > 70

DBP = diastolic blood pressure; HTN = hypertension; PMA = postmenstrual age; SBP = systolic blood pressure

fined as a systolic or diastolic reading approximately the 95th percentile for PMA,[23] as described in the case report[15] and as outlined in **Table 1**. Long-term hypertension was defined as a final chart diagnosis of hypertension at discharge.

PRES

As an additional outcome measure, magnetic resonance imaging (MRI) scans were also re-reviewed by a neuroradiologist (CY) for infants with sustained hypertension within 10 days of treatment. These infants had MRI scans completed as standard of care for clinical indications such as intraventricular hemorrhage, not to specifically look for PRES. MRI scans were evaluated for evidence of T2/FLAIR hyperintensities, particularly in the parietooccipital lobe cortex and subcortical white matter, although hyperintensities can also be present in basal ganglia, pons, and cerebellum. Hemorrhage associated with PRES was evaluated based on susceptibility-weighted imaging. The neuroradiologist also looked for associated diffusion restriction in larger areas of vasogenic edema, because this can occur in some cases.

Statistical Analysis

Data were summarized using percentages for categorical variables or means with standard deviations for continuous variables. Comparisons across the three treatment groups were performed using a chi-squared test or analysis of variance. Both a univariate and multivariate logistic regression model were fit to examine factors associated with sustained hypertension. Covariates were included in the multivariate model based on results from pairwise comparisons among treatment groups ($P < .20$, no adjustment for multiple comparisons). Comparisons of those who were included in the analytic sample versus those who were excluded, primarily due to not having sufficient blood pressure data, were performed using univariate logistic regression. Statistical significance was defined as a P value of .05 or less. Statistical analysis was performed using Stata 17 software (StataCorp LLC).

RESULTS

Overall, 158 infants were identified as having type 1 or type 2 ROP during the study period, and 137 patients were included in the final analysis. Twenty-one patients were excluded due to incomplete vital signs.

Table 2 categorizes patients by baseline demographics and neonatal comorbidities. There were no differences in baseline characteristics comparing infants treated with IVB to infants treated with laser, including no differences in the proportion infants in the IVB or laser groups who had hypertension noted prior to treatment. However, there was a higher proportion of patients in the type 2 ROP group without treatment who underwent patent ductus arteriosus ligation.

Among 94 treated infants, there was no difference in the proportion of infants who experienced short-term hypertension comparing those treated with IVB to those treated with laser: 41 of 67 infants who received IVB and 14 of 27 infants who received laser experienced short-term sustained hypertension in the first 90 days following treatment ($P = .406$, chi-squared test).

Among all infants with severe ROP (type 1 or type 2 ROP), there was no difference in odds of short-term hypertension compared to infants with type 1 ROP who received primary IVB treatment to either infants with type 1 ROP who received primary laser ($P = .47$) or infants with type 2 ROP who regressed spontaneously without treatment ($P = .40$). As shown in **Table 3**, the lack of association between IVB and short-term hypertension persisted after adjusting for other factors, including hypertension noted prior to treatment.

The majority of included infants, 78 of 137 (57%), experienced a period of short-term hypertension during 90 days after treatment for type 1

TABLE 2

Comparison of Demographic and Health Characteristics by Treatment Group

Characteristic	Type 1 (IVB)	Type 1 (Laser)	Type 2 (No Treatment)	Total	*P*[a]
Gender, n (%)					.15
Female	34 (50.8%)	8 (29.6%)	17 (39.5%)	59 (43.1%)	
Male	33 (49.3%)	19 (70.4%)	26 (60.5%)	78 (56.9%)	
Race/ethnicity, n (%)					.34
Non-Hispanic Black	40 (59.7%)	13 (48.2%)	23 (53.5%)	76 (55.5%)	
Non-Hispanic White	11 (16.4%)	7 (25.9%)	7 (16.3%)	25 (18.3%)	
Hispanic	13 (19.4%)	3 (11.1%)	11 (25.6%)	27 (19.7%)	
Other/unknown	3 (4.5%)	4 (14.8%)	2 (4.7%)	9 (6.6%)	
BPD, n (%)	59 (88.1%)	20 (80.0%)	33 (76.7%)	112 (83.0%)	.28
Severe IVH, n (%)	18 (27.3%)	2 (8.0%)	10 (23.8%)	30 (22.6%)	.14
PDA, n (%)	6 (9.1%)	2 (8.0%)	15 (35.7%)	23 (17.3%)	.001
UAC, n (%)	59 (88.1%)	24 (96.0%)	41 (95.4%)	124 (91.9%)	.28
RAS, n (%)	13 (19.4%)	7 (28.0%)	7 (16.3%)	27 (20.0%)	.50
Steroids, n (%)	52 (77.6%)	16 (64.0%)	31 (72.1%)	99 (73.3%)	.41
HTN in 3 days prior to index date, n (%)[b]	46/63 (73.0%)	16/22 (72.7%)	20/38 (52.6%)	82/123 (66.7%)	.09
Birth weight (g), mean (SD)	672 (162)	716 (158)	674 (169)	682 (163)	.47
Gestational age, mean (SD)	24.9 (2.0)	25.0 (1.7)	25.0 (1.3)	25.0 (1.7)	.95

BPD = bronchopulmonary dysplasia; IVB = intravitreal bevacizumab; PDA = patent ductus arteriosus requiring surgical ligation; RAS = renal artery stenosis; SD = standard deviation; severe IVH = severe intraventricular hemorrhage (grade 3 or grade 4); UAC = umbilical arterial catheter
[a]For comparison across three treatment groups based on chi-squared tests or analysis of variance.
[b]Denominator included due to only 123 patients having blood pressure data from the 3 days prior to index date.

TABLE 3

Logistic Regression Models of Sustained HTN Treatment Group, Unadjusted and Adjusted

Characteristic	Unadjusted Odds Ratio (95% CI)	Adjusted[a] Odds Ratio (95% CI)
Type 1 ROP–laser	0.68 (0.28, 1.68), *P* = .41	0.72 (0.26, 1.96), *P* = .52
Type 2 ROP–no treatment	0.73 (0.34, 1.58), *P* = .43	0.75 (0.31, 1.81), *P* = .53
Male gender (vs female)		1.00 (0.46, 2.15), *P* = .99
Race/ethnicity (vs White)		
Non-Hispanic Black		1.14 (0.40, 3.28), *P* = .81
Hispanic		1.26 (0.36, 4.44), *P* = .72
Other/unknown		2.77 (0.43, 18.06), *P* = .29
BPD		0.60 (0.21, 1.65), *P* = .32
Severe IVH		1.38 (0.54, 3.54), *P* = .50
PDA		1.06 (0.36, 3.10), *P* = .91
Steroids		1.31 (0.56, 3.03), *P* = .54
HTN in 3 days prior to index date (vs no)		
Yes		1.69 (0.74, 3.86), *P* = .21
Unknown		1.03 (0.25, 4.32), *P* = .97

BPD = bronchopulmonary dysplasia; HTN = hypertension; PDA = patent ductus arteriosus requiring surgical ligation; ROP = retinopathy of prematurity; severe IVH = severe intraventricular hemorrhage (grade 3 or grade 4)
[a]Covariates included were those with *P* < .20 based on pairwise comparisons between treatment groups (no multiple comparison adjustments).

TABLE 4

Comparison of Characteristics by Included and Excluded Group

Characteristic	Excluded	Included	Total	*P*[a]
Overall, N (%)	21 (13.3%)	137 (86.7%)	158	
Treatment group, n (%)				.31
IVB	8 (40.0%)	67 (48.9%)	75 (47.8%)	
Laser	7 (35.0%)	27 (19.7%)	34 (21.7%)	
Regressed	5 (25.0%)	43 (31.4%)	48 (30.6%)	
Sex, n (%)				.67
Female	8 (38.1%)	59 (43.1%)	67 (42.4%)	
Male	13 (61.9%)	78 (56.9%)	91 (57.6%)	
Ethnicity, n (%)				.94
Non-Hispanic White	3 (14.3%)	25 (18.2%)	28 (17.7%)	
Non-Hispanic Black	12 (57.1%)	76 (55.5%)	88 (55.7%)	
Hispanic	5 (23.8%)	27 (19.7%)	32 (20.3%)	
Other/unknown	1 (4.8%)	9 (6.6%)	10 (6.3%)	
Health characteristics, n (%)				
BPD	10 (58.8%)	112 (83.0%)	122 (80.3%)	.02
Severe IVH	1 (5.6%)	30 (22.6%)	31 (20.5%)	.13
PDA	3 (16.7%)	23 (17.3%)	26 (17.2%)	.95
UAC	16 (88.9%)	124 (91.9%)	140 (91.5%)	.67
RAS	4 (22.2%)	27 (20.0%)	31 (20.3%)	.83
Steroids	9 (50.0%)	99 (73.3%)	108 (70.6%)	.05
Birth weight (g), mean (SD)	770 (279)	682 (163)	691 (181)	.07
Gestational age, mean (SD)	25.0 (2.1)	25.0 (1.7)	25.0 (1.8)	.98

BPD = bronchopulmonary dysplasia; PDA = patent ductus arteriosus requiring surgical ligation; RAS = renal artery stenosis; severe IVH = severe intraventricular hemorrhage (grade 3 or grade 4); UAC = umbilical arterial catheter

[a]*P* from logistic regression models.

ROP (or the index date of 34 weeks PMA for type 2 ROP). Given the overall high rate of short-term hypertension in the study group, analyses were repeated restricting the definition of short-term hypertension to more than 3 days of sustained hypertension within 10 days of the procedure for type 1 ROP or index date for type 2 ROP. Restricting the outcome to within 10 days, 35 of 137 (26%) patients experienced short-term hypertension. From each group, this included 19 of 67 infants with type 1 ROP who received IVB, 5 of 27 infants with type 1 ROP who received laser, and 11 of 43 infants with type 2 ROP who regressed spontaneously. There was still no significant difference between groups (P = .61 from chi-squared test).

For long-term outcomes, there was no difference in the proportion of infants in each group who had a final chart diagnosis of hypertension. There were 6 of 77 patients in the IVB group and 2 of 39 patients in the laser group who had a final chart diagnosis of hypertension (P = .716, Fisher's exact test).

For the 35 patients with a diagnosis of short-term hypertension within 10 days of treatment, MRI scans were reviewed if otherwise completed as standard of care (n = 23, 66%). Only one patient had findings potentially consistent with PRES. However, the patient also had a history of hypoxic ischemic encephalopathy, and so the findings cannot be directly attributed to treatment. The neuroradiologist (CY) found areas of relatively diffuse cortical diffusion restriction involving the cerebral hemispheres bilaterally, although more conspicuous posteriorly in parietal more than occipital lobes, with likely sulcal effacement posteriorly and questioned associated mild T2 hyperintensity. This was most determined to be most likely sequela of the

patient's hypoxic ischemic encephalopathy, because PRES is less likely to restrict diffusion, and the patient had no basal ganglia findings, which may present in both conditions.

As shown in **Table 4**, there were few differences in baseline characteristics comparing the 137 included patients to 21 excluded patients whose medical records lacked complete daily nursing flow sheets with vital signs for review. Of note, there was a higher incidence of bronchopulmonary dysplasia ($P = .02$) and steroid treatment ($P = .05$) in the included patients compared to the excluded patients.

DISCUSSION

In this retrospective cohort study including 94 patients with treated ROP, there was no statistically significant difference in rates of short-term or long-term hypertension comparing infants treated with IVB to infants treated with laser. Overall, short-term hypertension is a common diagnosis among high-risk preterm infants with severe ROP, present in 57% of all included patients within 90 days after treatment for type 1 ROP or 34 weeks' PMA for infants with type 2 ROP. Although only 26% of infants experienced short-term hypertension within 10 days of treatment, none of these infants with MRI completed as standard of care (23 of 35) had vasogenic edema consistent with PRES. Although these findings cannot exclude the possibility of a small association, the lack of significant findings in this study reviewing frequent vital signs among patients with severe ROP over and 8-year time frame at our institution is reassuring.

Given the high rate of hypertension both before and after treatment, ROP may represent a systemic microvascular disease that is frequently associated with hypertension, and isolating the impact of IVB may be challenging. In fact, a study of adults who were former preterm infants found that severe ROP was an independent predictor of higher systolic blood pressure in adulthood.[24] If anything, this might bias the study toward finding increased rates of hypertension comparing type 1 ROP treated with IVB to type 2 ROP that regressed without treatment. The fact that no such difference was found provides further reassurance that a strong association between intravitreal IVB and systemic hypertension is unlikely. Further, these findings suggest that the 2021 study by Twitty et al's[19] high proportion of infants with hypertension may have been more related to the infants' ROP itself than to their IVB treatment.

The adult literature also reports multiple adverse effects in relation to systemic bevacizumab, with hypertension being the most reported.[16,25-27] Different theories on the pathophysiology of anti-VEGF–induced hypertension exist, but regardless hypertension is a common adverse effect of systemic bevacizumab and appears to be dose dependent.[27-29] A 2017 meta-analysis found that systemic bevacizumab increased the risk of cardiovascular events including arterial hypertension, ischemia, and bleeding.[29] Despite these concerns with systemic bevacizumab, findings on intravitreal bevacizumab have been reassuring in the adult literature. A 2021 meta-analysis in *JAMA Ophthalmology* found that intravitreal anti-VEGF agents did not have an associated increase in major cardiovascular events in adults.[30] However, a more recent study evaluating more than 1.7 million patients in the Veterans Health Administration found that patients with diabetes receiving anti-VEGF injections were more likely than those not receiving injections to experience systemic adverse events, including cardiovascular events, after adjusting for severity of diabetes.[31]

Additionally, the adult literature has described the development of PRES as a rare complication of systemic bevacizumab occurring anywhere from 16 hours to 1 year after medication administration.[16] In adults, the syndrome is notable for clinical findings of encephalopathy, headache, seizure, and associated neuroimaging findings of white matter changes and vasogenic edema on MRI, particularly in the parieto-occipital or posterior frontal distribution.[16,18,32,33] A significant finding of patients with PRES is the reversibility of MRI findings once the underlying condition has resolved and the offending agent has been removed.[32-34] To the best of our knowledge, there is only one case report describing an adult with choroidal neovascular membrane secondary to age-related macular degeneration who developed PRES after IVB therapy.[35]

Multiple studies have described an elevation of serum bevacizumab levels in neonates up to 60 days after IVB administration and an associated suppression of serum VEGF levels up to 8 weeks after treatment.[3,7,8] Although our findings are reassuring in that there was no statistically or clinically significant difference in rates of hypertension between the IVB and control groups, hypertension is a common finding among infants with severe ROP in general.

This retrospective study has inherent limitations. Complete nursing flow sheets including all vital signs were not available for some patients identified as having severe ROP, and 21 (13%) were excluded due to a lack of complete data. With a higher rate of BPD and steroid use among excluded patients, we cannot rule out that these patients were sicker than included patients. Fortunately, loss to follow-up was minimized because most patients remained in the neonatal intensive care unit for at least 1 month, or more, after treatment of ROP. Another potential limitation is error in charting vital signs, although this should not have a differential effect by treatment group. In addition, PRES could be underdiagnosed because 33% of patients with sustained hypertension within 10 days of treatment did not have MRI completed as standard of care. However, if the infant's course was otherwise reassuring enough that MRI was not clinically indicated, the clinical implications of any such findings might not have been meaningful.

One strength of this study was the use of vital signs from nursing flow sheets for 90 days, rather than only a chart diagnosis of hypertension, to minimize the chance we might miss subtle cases that were not captured by diagnostic codes. We also repeated this analysis over 10 days to ensure that we were not overly broad to dilute the potential association. As another measure of caution, a neuroradiologist reread MRI imaging specifically for the purpose of looking for PRES when the specific indications was a different diagnosis.

CONCLUSION

In the context of the 2020 case report[15] and follow-up 2021 study,[19] this study provides some reassurance that use of IVB for ROP has no obvious link to sustained hypertension or PRES. However, patients with severe ROP may be predisposed to hypertension in general, and short-term hypertension is a common finding in these patients regardless of treatment modality (or even regardless of treatment in patients with type 2 ROP). Future clinical trials in ROP might consider evaluating for hypertension and reviewing MRI imaging when available.

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