Neurodevelopmental Outcomes Following Bevacizumab Injections for Retinopathy of Prematurity

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abstract

BACKGROUND AND OBJECTIVE: Bevacizumab intravitreal injection, a vascular endothelial growth factor inhibitor, is used to treat retinopathy of prematurity (ROP). However, concerns have been raised regarding its systemic absorption and effect on developing tissues including brain. This study compared neurodevelopment at 18 months’ corrected age in preterm infants of <29 weeks’ gestation treated with bevacizumab versus laser ablation.

METHODS: Data from the Canadian Neonatal Network and the Canadian Neonatal Follow-Up Network databases were retrospectively reviewed. Infants born at <29 weeks’ in 2010–2011 with treated ROP were studied. Neurodevelopmental outcome at 18 months was assessed by using neurologic examination and the Bayley Scales of Infant and Toddler Development Third Edition. Regression analyses were performed.

RESULTS: Of 125 treated infants, 27 received bevacizumab and 98 laser. The bevacizumab group, compared with laser, obtained a median Bayley Scales of Infant and Toddler Development Third Edition motor composite score of 81 (interquartile range, 70–91) versus 88 (79–97), a language composite score of 79 (65–97) versus 89 (74–97), and a cognitive score of 90 (80–100) versus 90 (85–100). Difference was detected on the motor score only (P = .02). Odds of severe neurodevelopmental disabilities (Bayley scores <70, severe cerebral palsy, hearing aids, or bilateral blindness) was 3.1 times higher (95% confidence interval: 1.2–8.4) in infants treated with bevacizumab versus laser after adjusting for gestational age, gender, maternal education, Score for Neonatal Acute Physiology-II score, bronchopulmonary dysplasia, sepsis, and severe brain injury.

CONCLUSIONS: Preterm infants treated with bevacizumab versus laser had higher odds of severe neurodevelopmental disabilities. Further investigation on the long-term safety of antivascular endothelial growth factor treatment of ROP is needed.

WHAT’S KNOWN ON THIS SUBJECT: Intravitreal injection of bevacizumab is currently used to treat severe retinopathy of prematurity. Bevacizumab can diffuse into the systemic circulation and tissues. Long-term neurodevelopmental effects are unknown.

WHAT THIS STUDY ADDS: This retrospective observational study reveals that bevacizumab is associated with lower motor scores and higher rates of severe neurodevelopmental disabilities in preterm infants at 18 months of age.

Drs Morin and Luu conceptualized and designed the study and drafted the initial manuscript; Drs Superstein, Ospina, Lefebvre, Simard, and V. Shah reviewed and revised the research protocol and the manuscript; Dr P. Shah reviewed and revised the research protocol, supervised statistical analyses, and reviewed and revised the manuscript; Dr Kelly conceptualized and designed the study and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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Retinopathy of prematurity (ROP) is a vasculopathy of the developing vessels of the retina that occurs in neonates born preterm and is a well-recognized cause of pediatric blindness. Laser photoablation of the avascular retina is the standard of care for treatment of ROP and is highly successful. However, concerns regarding risks of intubation and sedation on neurodevelopment, adverse effects such as laser-induced myopia, visual field reduction, and suboptimal visual results in cases of posterior ROP, have motivated the search for alternative treatment.

Given that ROP is associated with high levels of vascular endothelial growth factor (VEGF) in the retina in later phases of the disease, using an anti-VEGF agent was an obvious prospect as new treatment of this disease. The landmark multicenter randomized controlled trial BEAT-ROP used intravitreal injection of bevacizumab to treat type 1 ROP (zone I or zone II posterior stage 3 with plus disease). Bevacizumab, compared with laser, reduced recurrence of ROP at 54 weeks' postmenstrual age for zone I ROP but not for zone II. At 2.5 years, infants treated with bevacizumab also had decreased rates of severe high myopia. Moreover, bevacizumab injection is a short procedure that only requires topical anesthetic, though some physicians, to minimize risk of lens injury due to infant movement, prefer using intravenous sedation. So far, the long-term safety of bevacizumab has not been examined. Given the prolonged half-life of bevacizumab and its potential antiangiogenic effect beyond the eye, it is crucial to document the whole-body effects of this drug, especially in preterm infants who are still undergoing organogenesis. Disturbance of vascular development at the cerebral level could be detrimental to brain development and potentially result in adverse motor, cognitive, and language outcomes. To our knowledge, only 1 case series including 13 very preterm infants revealed the long-term effect of bevacizumab, but used a screening developmental test and lacked a control group.

This study aimed to compare neurodevelopmental outcomes at 18 months' corrected age (CA) between preterm infants treated for severe ROP with bevacizumab versus laser ablation. We postulated that the advantage of using intravitreal bevacizumab to avoid intubation and sedation could be balanced by a hypothetical risk of an antiangiogenic systemic effect that could alter vascular brain development.

METHODS
Design and Study Participants
This is a retrospective analysis of data already collected as part of an observational cohort study from the Canadian Neonatal Network (CNN) and the Canadian Neonatal Follow-Up Network (CNFUN). The CNN and CNFUN maintain a national standardized database of neonatal diagnoses, treatments, and neurodevelopmental outcomes for all infants <29 weeks' gestational age (GA) admitted to all level III NICUs in Canada. We included all preterm infants with GA <29 weeks born between January 1, 2010, and September 30, 2011, with ROP, who required treatment during neonatal hospitalization, and who were seen for neurodevelopmental follow-up at 18 months' CA. Infants with major congenital anomalies were excluded. As ROP in itself is an independent predictor of long-term neurodevelopment and because we were interested in the long-term effect of VEGF blocker drugs, we divided participants according to whether they had received this specific treatment of ROP. Data collection was approved by the research ethics board at each site and parents/guardians of infants provided written consent to participate in the CNFUN database. This specific study protocol was also approved by CHU Sainte-Justine and Mount Sinai Hospital research ethics boards, and the steering committees of both networks.

Data Collection
Neonatal and demographic data were collected from the infant’s medical record by trained research personnel by using definitions from the CNN abstractor manual. Eligible participants were identified through the CNN database and linked to the CNFUN database. Data on ROP treatment were coded as a yes/no variable with information on type of treatment (VEGF blockers versus laser). VEGF blocker doses were collected, but incomplete in the majority of cases. The database did not contain any information on reasons for choosing VEGF blocker over laser. Data to compute the Score for Neonatal Acute Physiology-II (SNAP-II) score were collected during the first 12 hours of admission. SNAP-II is a measure of severity of illness; higher scores predict mortality in extremely preterm infants. Bronchopulmonary dysplasia was operationally defined as requirement for oxygen supplementation at 36 weeks’ GA or at the time of discharge to step down units.

At 18 months’ CA, infants were seen at 1 of the participating CNFUN sites for comprehensive neurodevelopmental assessment that included neurologic examination by a pediatrician. The Bayley Scales of Infant and Toddler Development Third Edition (Bayley-3) were administered by certified examiners. Hearing and visual function was determined through parental interviews and/or medical record review.
Outcomes

Primary outcome consisted of the Bayley-3 developmental composite scores. The Bayley-3 is a widely used recently validated and standardized developmental assessment for infants aged 1 to 42 months that yields 3 composite scores: cognitive, language, and motor.\textsuperscript{18} The mean is set at 100 with a SD of 15. If children could not be tested on the Bayley-3 due to severe neurodevelopmental delays, they were not given any score. Secondary outcomes included neurodevelopmental impairment defined as the presence of any of the following: cerebral palsy, sensorineural/mixed hearing loss, visual impairment, and developmental delay with any composite score <85. Severe neurodevelopmental disability was defined as presence of any of the following: cerebral palsy with a Gross Motor Function Classification Scale of 3, 4, or 5,\textsuperscript{19} requirement for hearing aids or cochlear implants, bilateral visual impairment diagnosed by an ophthalmologist as presence of macular drag, traction or detachment, visual acuity of 20/70 or worse, or severe developmental delay with any composite score <70.

Statistical Analyses

Infant demographic characteristics, neonatal data, and neurodevelopmental outcomes of the 2 groups of infants were compared by using Pearson’s $\chi^2$ test (categorical) and Student’s $t$ test (continuous) for variables normally distributed, and with Fisher’s exact test (categorical) and Wilcoxon Rank Sum test (continuous) for variables not normally distributed. We adjusted for confounding factors with unequal distribution between the 2 treatment groups by using logistic regression analyses. These factors included GA, male gender, maternal education, SNAP-II score, bronchopulmonary dysplasia, sepsis, and grade 3 and 4 intraventricular hemorrhage. Statistical analyses were carried out by using SAS version 9.3 (SAS Institute, Inc, Cary, NC).

RESULTS

During the study period, 3233 preterm infants born <29 weeks’ GA were admitted to 1 of the participating NICUs of the CNN, of which 1154 were diagnosed with ROP (Fig 1). Among them, 174 were treated for ROP: 37 had intravitreal bevacizumab and 137 received retinal laser photoablation. Follow-up data were available for 125 infants (bevacizumab, $n = 27$; laser, $n = 98$). The 49 infants with no follow-up data were comparable to participants included in the study in terms of GA, birth weight, oxygen need at 36 weeks, sepsis, intraventricular hemorrhage, type of ROP, and maternal age. However, participants were more likely to be girls ($P = .06$), to have been exposed to antenatal steroids ($P = .04$), and to have patent ductus arteriosus ligation ($P = .05$) compared with those lost to follow-up.

Table 1 compares neonatal characteristics of preterm infants who were treated with bevacizumab versus those who were treated with laser. Of note, 3 infants had both bevacizumab and laser treatment; these were included in the bevacizumab group. GA and birth weight were similar between the 2 groups. Infants treated with bevacizumab appeared sicker upon admission as shown by their higher SNAP-II score. There was a trend toward a higher proportion of boys and a longer neonatal hospitalization, although this was not statistically significantly different. Rates of neonatal complications were similar. Infants in the bevacizumab group had more severe ROP at the time of treatment as shown by higher rates of posterior and plus disease. At least 11 infants who received laser ablation did not fulfill current recommendations for ROP treatment.\textsuperscript{20}

Table 2 reveals neurodevelopmental outcomes at 18 months’ CA. Mean CA of assessment was 19 ± 1.3 months. Bayley-3 assessment could not be completed at all in 10 infants (bevacizumab, $n = 1$; laser $n = 9$). Reasons included the following: severe developmental delays ($n = 3$ including 1 infant treated with bevacizumab), blindness or deafness ($n = 2$), uncooperative ($n = 1$), and unknown ($n = 3$). Median motor scores were lower in infants who had received bevacizumab. No difference in cognition and language was detected between the 2 groups. Rates of neurodevelopmental impairment and severe neurodevelopmental disability were higher in the bevacizumab group. In general, bevacizumab-treated infants were 2 to 3 times more likely to display unfavorable developmental outcomes compared with those who had received laser, but after adjusting for confounders, only risk of severe neurodevelopmental disability remained statistically significant.
**TABLE 1** Neonatal Characteristics of Infants Treated With Bevacizumab Versus Laser

<table>
<thead>
<tr>
<th></th>
<th>Bevacizumab (N = 27)</th>
<th>Laser (N = 98)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA, mean (SD), wk</td>
<td>24.9 (1.5)</td>
<td>24.7 (1.3)</td>
<td>.54</td>
</tr>
<tr>
<td>Birth weight, mean (SD), g</td>
<td>739 (172)</td>
<td>714 (140)</td>
<td>.44</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>16 (59)</td>
<td>41 (42)</td>
<td>.11</td>
</tr>
<tr>
<td>Multiple, n (%)</td>
<td>9 (33)</td>
<td>29 (30)</td>
<td>.71</td>
</tr>
<tr>
<td>Maternal age, mean (SD), y</td>
<td>29.8 (6.8)</td>
<td>29.9 (4.8)</td>
<td>.94</td>
</tr>
<tr>
<td>Maternal education, n (%)</td>
<td>Less than high school</td>
<td>7 (29)</td>
<td>18 (20)</td>
</tr>
<tr>
<td></td>
<td>High school</td>
<td>2 (8)</td>
<td>9 (10)</td>
</tr>
<tr>
<td></td>
<td>Some college and above</td>
<td>15 (63)</td>
<td>65 (71)</td>
</tr>
<tr>
<td>Antenatal steroids, n (%)</td>
<td>25 (100)</td>
<td>87 (91)</td>
<td>.20</td>
</tr>
<tr>
<td>SNAP-II score, median (IQR)</td>
<td>24 (19–31)</td>
<td>19 (13–28)</td>
<td>.03</td>
</tr>
<tr>
<td>Supplemental oxygen at 36 wk CGA, n (%)</td>
<td>20 (74)</td>
<td>76 (78)</td>
<td>.70</td>
</tr>
<tr>
<td>Postnatal steroid use, n (%)</td>
<td>19 (70)</td>
<td>60 (61)</td>
<td>.38</td>
</tr>
<tr>
<td>Patent ductus arteriosus ligation, n (%)</td>
<td>8 (30)</td>
<td>40 (41)</td>
<td>.29</td>
</tr>
<tr>
<td>Late-onset sepsis, n (%)</td>
<td>15 (56)</td>
<td>47 (48)</td>
<td>.48</td>
</tr>
<tr>
<td>ROP, n (%)</td>
<td>Grade 1–2</td>
<td>10 (37)</td>
<td>34 (35)</td>
</tr>
<tr>
<td></td>
<td>Grade 3–4</td>
<td>2 (7)</td>
<td>12 (12)</td>
</tr>
<tr>
<td></td>
<td>Zone II no plus with stage 1, 2, 3</td>
<td>0 (0)</td>
<td>5 (5.1)</td>
</tr>
<tr>
<td></td>
<td>Zone I plus with stage 1, 2, 3; no plus stage 3</td>
<td>5 (19)</td>
<td>7 (7)</td>
</tr>
<tr>
<td></td>
<td>Zone II no plus with stage 1, 2, 3</td>
<td>0</td>
<td>8 (8)</td>
</tr>
<tr>
<td></td>
<td>Zone II plus with stage 1, 2, 3</td>
<td>21 (78)</td>
<td>63 (64)</td>
</tr>
<tr>
<td></td>
<td>Zone III</td>
<td>1 (4)</td>
<td>8 (8)</td>
</tr>
<tr>
<td></td>
<td>Stage 4, 5</td>
<td>0</td>
<td>2 (2)</td>
</tr>
<tr>
<td></td>
<td>Incomplete informationa</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Duration of neonatal stay, mean (SD), d</td>
<td>139 (52)</td>
<td>128 (42)</td>
<td>.23</td>
</tr>
</tbody>
</table>

CGA, corrected gestational age; IQR, interquartile range.

a Six cases of ROP with stages 1 to 2 and missing information on zone or plus disease. Four cases of stage 3 ROP with missing information on zone and plus disease.

**TABLE 2** Comparison of Growth and Neurodevelopmental Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Bevacizumab (n = 27)</th>
<th>Laser (n = 98)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted ORa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, mean (SD), kg</td>
<td>9.9 (1.4)</td>
<td>10.2 (1.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length, mean (SD), cm</td>
<td>79.7 (4.1)</td>
<td>79.5 (3.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head circumference, mean (SD), cm</td>
<td>46.5 (1.6)</td>
<td>46.3 (1.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral palsy, n (%)</td>
<td>&lt;5b</td>
<td>11 (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hearing aids, n (%)</td>
<td>&lt;5b</td>
<td>6 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any visual problem, n (%)</td>
<td>13 (48)</td>
<td>42 (44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral blindness, n (%)</td>
<td>&lt;5b</td>
<td>5 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayley-3 scores, median (IQR)</td>
<td>90 (80–100)</td>
<td>90 (85–100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognition</td>
<td>90 (85–97)</td>
<td>88 (74–97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Language composite</td>
<td>81 (70–91)</td>
<td>88 (73–97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor composite</td>
<td>11/26 (42)</td>
<td>22/89 (25)</td>
<td>2.2 (0.9–5.8)</td>
<td>2.6 (0.9–7.7)</td>
</tr>
<tr>
<td>Bayley-3 scores &lt;85, n (%)</td>
<td>15/25 (60)</td>
<td>35/85 (41)</td>
<td>2.1 (0.9–5.3)</td>
<td>2.0 (0.7–5.3)</td>
</tr>
<tr>
<td>Cognition</td>
<td>21/25 (84)</td>
<td>26/86 (30)</td>
<td>2.5 (1.0–6.2)</td>
<td>2.3 (0.8–5.6)</td>
</tr>
<tr>
<td>Neurodevelopmental impairment, n (%)</td>
<td>21 (78)</td>
<td>55 (56)</td>
<td>2.7 (1.0–7.4)</td>
<td>3.0 (0.97–9.0)</td>
</tr>
<tr>
<td>Severe neurodevelopmental disability, n (%)</td>
<td>14 (52)</td>
<td>28 (29)</td>
<td>2.7 (1.1–6.4)</td>
<td>3.1 (1.2–8.4)</td>
</tr>
</tbody>
</table>

CI, confidence interval; IQR, interquartile range; OR, odds ratio.

a Adjusted for GA, male gender; maternal education, SNAP-II score, bronchopulmonary dysplasia, sepsis, and grade 3 or 4 intraventricular hemorrhage.

b According to network policy, any cell with values <5 is suppressed to avoid possibility of reidentification.

DISCUSSION

This observational study exploring the long-term neurodevelopmental effect of bevacizumab identified that bevacizumab was associated with lower motor scores and higher rates of severe neurodevelopmental disability in extremely preterm infants at 18 months’ CA. Since the BEAT-ROP study, intravitreal bevacizumab has been used increasingly as an off-label treatment of ROP.

The pathophysiology of ROP in its late phase is thought to be related to high levels of VEGF. This occurs after initial retinal hypoxia leads to upregulation of VEGF that consequently induces excessive neovascularisation.7, 21, 22 Although blocking VEGF locally may confer benefit, blocking its effects systemically may have unanticipated consequences especially in infants because VEGF is critical for neurogenesis during brain development.23 The pharmacokinetics and systemic safety of intraocular anti-VEGF agents are just being unraveled. Kong et al24 measured serum bevacizumab levels in 24 extremely preterm infants treated with intravitreal injections for type 1 ROP. Peak bevacizumab serum concentrations were observed at 14 days postinjection. In addition, bevacizumab was still detectable in the blood for as long as 60 days after treatment with a half-life of 21 days. Of concern, a recent study conducted in 6 infants with ROP revealed that plasma VEGF concentrations 1 to 7
weeks after bevacizumab injections were significantly lower than before treatment, suggesting that intraocular injections of bevacizumab can significantly suppress systemic VEGF. Larger series conducted in 44 adults also revealed reduced VEGF plasma level for as long as 1 month after bevacizumab intraocular injection in patients with age-related macular degeneration or diabetic macular edema.

Although mounting evidence points toward potential systemic action, there has been limited research examining developmental risk for infants who received bevacizumab during their neonatal hospitalization. Only 1 case series including 13 very preterm neonates (≤32 weeks' GA) revealed the long-term effect of bevacizumab on visual acuity and child development. At 5 years, only 1 child had poor neurodevelopment on the basis of the Ages and Stages Questionnaire, a developmental screening measure. Our study is the first to document long-term neurodevelopmental effects of bevacizumab by using a standardized and well-validated developmental examination and to compare outcomes with a contemporary group of preterm infants who received laser treatment of ROP.

Bayley-3 language and motor composite scores were consistently lower in the bevacizumab-treated group, although the difference only reached statistical significance for motor development. In contrast, both groups achieved similar cognitive scores. Rates of severe neurodevelopmental disorders were also higher in the bevacizumab group (51.9% vs 28.6%). It is unclear as to the reason for the selective vulnerability of motor development. Brain development continues to be an active process during the first 18 months of life with significant changes and rapid gains particularly in motor skills: infants evolve from lying on their back to walking and climbing up stairs within a short period of time. Therefore, any events disturbing cerebral development may be first observed with delays in this domain before abnormalities are uncovered in language or cognition. It is also possible that our study was insufficiently powered to detect differences in the other developmental domains or could have detected differences in motor scores by chance alone.

Strengths of our study include a cohort followed prospectively from neonatal discharge to infancy, national data set, and standardized assessment. In addition, comparison with laser-treated neonates provides a like-to-like comparison as both groups of infants are at high risk of disability. However, the observational nature of this study makes confounding by indication a possibility. We did not have any information regarding protocol used to decide upon intervention nor reasons that could have motivated choosing bevacizumab over laser. Indeed, choice of ROP treatment could have been influenced by the infant's overall medical condition, with sicker patients being better candidates for a procedure that does not require general anesthesia, notably those with more severe respiratory compromise, which is known to be associated with higher risk of neurodevelopmental impairment. To partially overcome this issue, statistical analyses were carried out with adjustment for covariates associated with adverse outcomes including oxygen requirement, but residual confounding cannot be excluded. As a matter of fact, infants treated with bevacizumab displayed more severe ROP, which is also associated with adverse neurodevelopmental outcome. Although the cohort was prospectively followed, data on ROP treatment were retrospectively collected and therefore, treatment details such as bevacizumab dose were not always reported, thus hindering our ability to characterize further our population. This study was also limited by the percentage of infants lost to follow-up or who refused to participate. In addition, follow-up was incomplete with a retention rate of 72%. However, characteristics of nonparticipants were equally distributed between the 2 groups making selection bias less likely. Despite the small numbers, this is the largest population-based study to date evaluating neurodevelopmental outcome after bevacizumab injection.

**CONCLUSIONS**

Intravitreal bevacizumab to treat severe ROP may be associated with...
higher rates of neurodevelopmental impairment in comparison with laser therapy. This study raises some concerns regarding the long-term safety of anti-VEGF treatment and calls for the importance of conducting research that considers the potential systemic effects of new medications used in preterm infants on organ development. Bevacizumab as well as aflibercept and ranibizumab or any other anti-VEGF being used to treat ROP need long-term monitoring to ensure that benefits are not outweighed by unanticipated adverse outcomes.

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ABBREVIATIONS

Bayley-3: Bayley Scales of Infant and Toddler Development Third Edition
CA: corrected age
CNFUN: Canadian Neonatal Follow-Up Network
CNN: Canadian Neonatal Network
GA: gestational age
ROP: retinopathy of prematurity
SNAP-II: Score for Neonatal Acute Physiology-II
VEGF: vascular endothelial growth factor
REFERENCES


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