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# Neurodevelopmental Outcomes after Bevacizumab Treatment for Retinopathy of Prematurity

## A Meta-analysis

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***Purpose:*** To evaluate neurodevelopmental outcomes after intravitreal bevacizumab (IVB) therapy in retinopathy of prematurity (ROP) infants compared with those not exposed to IVB.

***Clinical Relevance:*** The primary concern regarding IVB treatment of ROP is the potential systemic side effects, especially the risk of causing severe neurodevelopmental impairment (sNDI). Results regarding neurodevelopmental outcomes after IVB therapy are conflicting.

***Methods:*** We conducted a meta-analysis and searched PubMed, Embase, and Web of Science for related publications from inception through March 12, 2020. The eligibility criteria were as follows: comparative studies of ROP patients that (1) included IVB as a treatment arm, (2) included a control group without bevacizumab treatment, and (3) reported on at least 1 neurodevelopmental outcome, such as sNDI, Bayley Scales of Infant and Toddler Development, Third Edition (Bayley III), composition scores, or cerebral palsy (CP). The primary outcome was sNDI, with the odds ratio (OR) calculated. Secondary outcomes were mean differences (MDs) for cognitive, language, and motor scores (Bayley III) and OR for CP. The quality of evidence was assessed using the Grades of Recommendation, Assessment, Development, and Evaluation approach.

***Results:*** Eight studies, 6 including laser-controlled ROP infants and 2 including ROP infants not requiring treatment, were included. The weighted OR for sNDI in the IVB group was 1.39 (95% confidence interval [CI], 0.98−1.97). The weighted MDs were −1.92 (95% CI, −4.73 to 0.88), −1.32 (95% CI, −4.65 to 1.99), and −3.66 (95% CI, −6.79 to −0.54) for cognitive, language, and motor scores in Bayley III, respectively. The OR for CP was 1.20 (95% CI, 0.56−2.55). No differences were observed between the preset subgroups comprising laser-controlled ROP infants and ROP infants not requiring treatment. The current quality of evidence was rated as low (sNDI and all Bayley III scores) to very low (CP).

***Conclusions:*** Risk of sNDI was not increased in ROP patients after IVB treatment. Bayley III scores were similar in the IVB and control groups, except for a minor difference in motor performance. These findings suggest that the risk of additional sNDI after IVB treatment is low. Randomized trials are warranted to provide a higher quality of evidence. *Ophthalmology 2021;128:877-888 © 2020 by the American Academy of Ophthalmology*

*Supplemental material available at www.aaojournal.org.*

Retinopathy of prematurity (ROP) is a leading cause of blindness in children worldwide, with 32 300 preterm infants exhibiting any degree of visual impairment in 2010.[1] Recently, a third epidemic of blindness resulting from ROP was reported in Eastern Europe, Latin America, and East and South Asia and may occur in Africa.[2] Retinopathy of prematurity affects developing and developed countries. According to a health care database, ROP incidence in the United States increased from 2000 through 2012, with a peak of 19.88% during this period.[3] The improved survival of infants born extremely preterm and with extremely low birth weights is believed to contribute to the increasing ROP incidence and the increasing number of patients requiring treatment for type 1 ROP.[1,2]

Retinopathy of prematurity treatment has evolved in recent years. Modern treatment guidelines for ROP were established based on the results of the Early Treatment of ROP study, which used laser photocoagulation as the standard treatment for high-risk ROP patients and showed a reduced incidence of unfavorable outcomes.[4] More recently, the Bevacizumab Eliminates the Angiogenic Threat of ROP (BEAT-ROP) trial demonstrated the superior outcomes of intravitreal bevacizumab (IVB), an anti−vascular endothelial growth factor (VEGF) agent, in type 1 ROP patients compared with laser treatment.[5] In addition, anti-VEGF


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therapy has been reported to result in a relatively low refractive error[6] and favorable foveal development[7]; therefore, it has become another first-line treatment for selective conditions in type 1 ROP.[8] However, some concerns exist regarding the use of anti-VEGF injections in preterm babies. Wu et al[9] reported that serum VEGF, a key mediator in organogenesis,[10,11] was suppressed for 2 months after a single dose of bevacizumab. One of the main drawbacks of using anti-VEGF in the pediatric population is the uncertainty of the long-term systemic side effects of this treatment, especially its effects on neurodevelopment.[6,8,12,13]

Neurodevelopmental impairment (NDI) is a notable complication in preterm infants, and it can have a lifelong effect on their quality of life. Additionally, the incidence of NDI increases as the gestational age (GA) decreases.[14] Several studies reported neurodevelopmental outcomes in ROP patients who underwent IVB treatment; however, these studies provided inconsistent conclusions.[15–25] The increased risk of severe NDI (sNDI)[19] and poor cognitive outcomes[23] after IVB treatment have been reported; however, some studies demonstrated no differences in these aspects between the IVB and control groups. In addition, most such studies are limited by a small sample size; therefore, further research is needed to understand better the potential systemic effects of anti-VEGF therapy on preterm development. The present meta-analysis evaluated the effect of IVB therapy on the neurodevelopmental outcomes of preterm infants who had undergone treatment for ROP, including the risk of sNDI and cerebral palsy (CP) and the language, motor, and cognitive performance of these patients in early childhood.

## Methods

### Eligibility Criteria for Considering Studies for This Review

We performed a systemic review and meta-analysis in accordance with our preset protocol (Appendix 1, available at www.aaojournal.org) to prevent bias resulting from post hoc decisions. This study adhered to the tenets of the Declaration of Helsinki. The institutional review board of the National Taiwan University Hospital exempted the current study from review. The requirement for informed consent was waived because of the retrospective nature of the study. The eligibility criteria were as follows: a comparative study that (1) recruited ROP patients, (2) included IVB in at least 1 treatment arm, (3) included a control group that did not receive anti-VEGF therapy, and (4) reported at least 1 outcome of interest, including sNDI incidence, scores of the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley III),[26] at corrected age after 1 year of age, and CP incidence.

### Search Methods for Identifying Studies

We conducted a systematic search using the PubMed, Embase, and Web of Science databases for studies written in any language and published before March 12, 2020. The following key words were used: [bevacizumab OR avastin] AND [retinopathy of prematurity] AND [neurodevelopment OR neurodevelopmental OR development OR developmental]. The detailed search strategies and results are presented in Table S1 (available at www.aaojournal.org). In addition, we reviewed the reference lists of all selected articles to identify other potentially relevant studies.

### Study Selection

Two investigators (C.-Y.T. and T.-T.L.) independently reviewed the titles and abstracts of all identified studies. The full texts of all potentially eligible articles were then evaluated further to ensure that the studies met the eligibility criteria. Articles not written in English and without full-text translations as well as meeting abstracts without full text and complete reports were excluded. Duplications also were excluded; in cases of duplications, the latest report of a single study was included in our analysis. Disagreements were resolved through discussion with a third investigator (P.-T.Y.).

### Data Collection and Risk-of-Bias Assessment

For each enrolled study, the study design, patient characteristics, intervention and control, length of follow-up, and outcomes of interest were extracted independently for further analysis by 2 reviewers (C.-Y.T. and T.-T.L.). In line with previous studies,[19,22] sNDI was diagnosed if any of the following conditions were present: the worst composition score (in any one of cognitive, language, or motor score) in Bayley III was less than 70, severe hearing loss was apparent (i.e., requiring cochlear implant or hearing aids), or severe vision loss was identified (i.e., bilateral visual impairment, macular dragging, or retinal detachment). For studies that included mild ROP infants without treatment as a control group, visual impairment was excluded from the diagnostic criteria for sNDI.[21,22] For studies that reported Bayley III scores at multiple time points, the results at 18 to 24 months of the corrected age were analyzed. When multiple control groups were included, the one with the lowest baseline difference compared with the IVB group and the lowest risk of bias was used for the meta-analysis. The corresponding authors of all included studies were contacted, and 5 of them replied, of whom 2 provided the complete original data and 1 provided the data of the IVB group. The quality of each included observational study was evaluated using the Newcastle-Ottawa scale.[27]

### Data Synthesis and Analysis

Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using the Mantel–Haenszel method to assess the risks of sNDI and CP in the bevacizumab-treated and control groups. For each composition score of Bayley III, including those for cognitive function, language, and motor function, the mean difference (MD) was reported with 95% CI based on an inverse-variance, weighted meta-analysis. A random-effects model analysis was performed for all outcomes, and heterogeneity was quantified using the $I^2$ statistic. A fixed-effect meta-analysis was performed as a sensitivity analysis. Because a baseline difference was expected between studies that used laser as the control and those that used nontreatment as the control, a preset subgroup was applied to all analyses according to the control group. Additional post hoc subgroup analyses were performed to evaluate the potential confounding effects of GA, birth weight, and study design. Studies were categorized according to the presence of a GA threshold as the study's inclusion criteria, the average GA or birth weight in the IVB group, or the study design. In addition, forest plots were constructed in each analysis. In the studies that reported Bayley III scores as medians and ranges[20] or interquartile ranges,[19,21,24] the scores were converted to means and standard deviations (SDs) before the meta-analysis in accordance with previously reported statistical methods,[28] except for 1 study,[21] whose original data were available and therefore used for the

meta-analysis. Sensitivity analysis also was performed using only published data to evaluate potential bias related to the use of original data. Furthermore, publication bias was assessed using funnel plots. To evaluate the quality of the evidence for each outcome of interest, we used the Grades of Recommendation, Assessment, Development, and Evaluation system,[29] which includes the following aspects: study limitations, consistency, directness, precision, and publication bias; it also provides a final quality assessment (very low, low, moderate, or high) for each outcome. All statistical analyses were performed using Review Manager (RevMan) software version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration) and SPSS software version 22.0 (IBM Corp.).

## Results

### Study Characteristics and Risk-of-Bias Assessment

The database search identified 399 records, and 10 comparative studies ultimately were found. Of these 10 studies, 8[18–25] were included in the final analysis, and 2[16,17] were excluded because of the lack of reporting on any of our desired outcomes of interest. Figure 1 shows the search findings, and Table 2 presents the study characteristics. All included studies were observational studies, and 1 study[20] enrolled patients from a previous randomized controlled trial (RCT), the BEAT-ROP study.[5] The bevacizumab dose was 0.625 mg/0.025 ml in 4 of the included studies[20–22,24]; the remaining studies did not specify the dose or dosage. All studies used bevacizumab monotherapy for the treatment group, except for 1 study[18] that used laser combined with bevacizumab for the treatment group. Regarding the control groups, 5 studies[18–20,24,25] used laser monotherapy as the control and Natarajan et al[23] used laser treatment or cryotherapy, Chang et al[21] enrolled ROP patients who did not require treatment as controls, and Fan et al[22] compared the treatment group to infants without ROP and those with ROP but who required no treatment. Most of the included participants received neurodevelopmental evaluation at 18 to 24 months of corrected age. The results of the risk-of-bias assessment using the Newcastle-Ottawa Scale are summarized in Table S3 (available at www.aaojournal.org).

### Severe Neurodevelopmental Impairment

Of the 8 studies included in the analysis, 5[19,22–25] reported outcomes related to sNDI, and the results of 1 study[21] were available by accessing the original dataset. Severe NDI risk did not differ significantly between the IVB and control groups, with an overall OR for sNDI of 1.39 (95% CI, 0.98−1.97; test for overall effect: $Z = 1.84$, $P = 0.07$). No heterogeneity was detected ($I^2 = 4\%$), and the results remained true in both subgroups: laser and nontreatment as the control (Fig 2). In the sensitivity analysis, the ORs were similar after the result accessed through the original dataset[21] had been removed (OR, 1.51 [95% CI, 0.98−2.30]) and when the fixed-effect model was used (OR, 1.37 [95% CI, 0.99−1.89]).

### Bayley Scales of Infant and Toddler Development, Third Edition, Composition Scores

In all of the 8 included studies, Bayley III composition scores at 18 to 24 months of corrected age were available; 3 studies[18,22,25] reported the scores in means with SDs, 1 study[23] reported the scores in means with standard errors, 1 study[20] reported the scores in medians and ranges, and 3 studies[19,21,24] reported the scores in medians and interquartile ranges (full access to the original data was possible in 1[21] of these 3 studies). All analyses were performed after the results had been converted to means with SDs; the results are shown in Figure 3.

**Cognitive Function.** The mean cognitive scores of Bayley III did not differ significantly between the IVB and control groups (MD, −1.92 [95% CI, −4.73 to 0.88]). No evident heterogeneity was observed ($I^2 = 0\%$). Similar results were found in both the laser-controlled and no treatment-controlled subgroups (MD, −1.69 [95% CI, −4.92 to 1.55] and −2.63 [95% CI, −8.24 to 2.99], respectively).

**Language.** No significant difference was observed in language scores between the IVB and control groups (MD, −1.32 [95% CI, −4.65 to 1.99]). No heterogeneity was detected ($I^2 = 0\%$). These results did not differ significantly when IVB was compared with laser treatment (MD, −1.38 [95% CI, −5.52 to 2.75]) or with nontreatment (MD, −1.21 [95% CI, −6.74 to 4.32]).

**Motor Function.** A minor but significant difference was observed in the motor scores of Bayley III between the IVB and control groups (MD, −3.66 [95% CI, −6.79 to −0.54]). No heterogeneity was observed ($I^2 = 0\%$). A similar trend favoring the control group was observed in both subgroups, but without statistical significance (control: laser treatment MD, −3.35 [95% CI, −6.97 to 0.27]; no treatment MD, −4.60 [95% CI, −10.82 to 1.63]).

**Sensitivity Analysis.** The MDs were the same under fixed-effect meta-analysis. We replaced the calculated means and SDs from the original data of Chang et al[21] with those converted from medians and interquartile ranges and found no difference in the results of the meta-analysis regarding cognitive function (−1.92 [95% CI, −4.73 to 0.88]), language (−1.29 [95% CI, −4.61 to 2.04]), or motor function (−3.65 [95% CI, −6.79 to −0.52).

### Cerebral Palsy

Three studies[19,20,24] reported CP incidence in their original reports; the numbers of CP infants were accessed through the original dataset of another study.[21] Cerebral palsy risk was similar in the IVB and control groups (OR, 1.20 [95% CI, 0.56−2.55]; Fig 4). No heterogeneity was detected between the two subgroups ($I^2 = 0\%$). In 1 study,[19] the number of CP infants in the IVB group was reported as "<5," in accordance with the policy of the journal in question; therefore, we inserted "0 to 4" for the sensitivity analysis and found no difference regarding the conclusion; the results remained the same during the sensitivity analysis when only published data were used and when the fixed-effect model was applied.

### Post hoc Analysis Based on Gestational Age, Birth Weight, and Study Design

The results of post hoc subgroup analyses are summarized in Table S4 (available at www.aaojournal.org). Three studies included a GA limit in their inclusion criteria (GA <27 weeks[20,23] or <29 weeks[19]). The average GA in the IVB group was 25 weeks or less in 6 studies[19–21,23–25] (range, 24.4−25.0 weeks), and these groups also had an average birth weight of 800 g or less (range, 630−739 g); the other 2 studies[18,22] had an average GA of more than 25 weeks (range, 26.4−27.3 weeks) and average birth weight of more than 800 g (range, 833−1017 g) in the IVB group. Only 1 of the enrolled studies was a prospective study.[22] The risk of sNDI and CP and the average Bayley III scores in each domain were similar between the IVB and control groups in all subgroups, except for a significant difference in the motor scores of Bayley III in the retrospective studies[18–21,23–25]

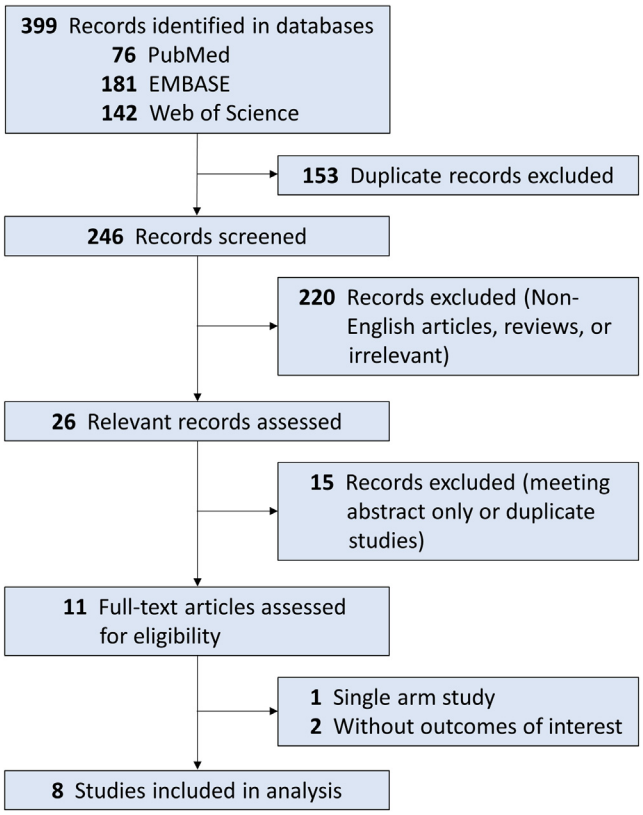


**Figure 1.** Flow diagram showing study selection for inclusion in the meta-analysis.

(MD, −3.56 [95% CI, −7.00 to −0.13]), and this result was in line with that of the original analysis. The results of the meta-analysis in all outcomes of interest revealed no difference between the subgroups in any subgroup analysis.

### Quality of the Evidence

Table 5 summarizes the results of the quality of the evidence according to the Grades of Recommendation, Assessment, Development, and Evaluation system. Generally, the quality of evidence was rated as low (for sNDI and all Bayley III composition scores) to very low (for CP) because only observational studies were present during the literature search. The quality of evidence for CP was downgraded because of the small number of included studies and participants, leading to concerns of imprecision.

## Discussion

To the best of our knowledge, there has not been another meta-analysis investigating the neurodevelopmental outcomes of infants after IVB treatment. The results suggest that IVB treatment did not significantly increase sNDI or CP risk and that cognitive function and language performance at approximately 2 years of corrected age were similar between infants who had undergone IVB treatment and the corresponding controls. A slightly more favorable Bayley III motor score was noted in the control group compared with the IVB group; however, the clinical significance of this difference of 3.7 between the motor scores remains unclear.

The systemic absorption and potential side effects of IVB long have been major concerns between physicians favoring IVB treatment and those favoring laser treatment.[12,13] The serum concentration of VEGF can be suppressed after a single dose of IVB,[9,30–32] and animal studies reported the adverse effects of serum VEGF depletion on kidney and lung development.[33–35] Nevertheless, most related clinical studies reported similar levels of risk of developmental impairment between IVB treatment and control groups.[16–18,20–22,24,25] Owing to their small sample size, the power of these studies to detect differences between IVB and control groups may be low.[19] The results of the current meta-analysis, which analyzed more than 700 infants, supported previous conclusions that IVB treatment does not increase the risk of impairment. In addition, the low heterogeneity in our analysis further strengthened the validity of our results.

However, the minor difference in the motor scores between the IVB and control groups raised some concerns. Each composite score in Bayley III showed a mean of 100 and an SD of 15 based on the norm-referenced index,[26] and 7.5 (half of the SD) frequently is used as a clinically important difference.[36,37] Therefore, the aforementioned difference of 3.7 in the current meta-analysis may not be clinically significant. Nonetheless, Morin et al[19] reported a relatively low motor score and a relatively high rate of sNDI; those researchers suspected that a delay in motor function is the first manifestation of disturbed cerebral development. The role of VEGF during brain development, including the migration of neural progenitors and vascular development, has been reported in previous studies.[38–40] In addition, neurogenesis may continue in extremely preterm babies[41]; therefore, the brain may be vulnerable to changes in the VEGF level. However, an in vivo study found no changes in VEGF or VEGF receptor expression in the brains of rat pups, although VEGF had been suppressed systemically for 14 days.[35] Further research is required to elucidate the precise role of anti-VEGF therapy on preterm brain development. Another possible reason for the inferior motor function reported in the study by Morin et al[19] may be the imbalance of baseline conditions between IVB-treated and laser-treated preterm infants.[42]

Neurodevelopmental impairment occurs in 7% of all survived preterm infants[14] and generally includes CP, visual and hearing loss, and developmental delay,[24,43] with the delay being evaluated through clinical tests such as Bayley III. Furthermore, in these preterm infants, the developments of ROP and NDI share common risk factors, including low GA and birth weight.[44–46] The incidence of NDI increased from 5% among infants born at 32 to 36 weeks' GA to 24.5% among those born at 28 to 31 weeks' GA, and further to 52% among those born before 28 weeks' GA (extremely preterm).[14] These extremely preterm infants also are at higher risk of aggressive posterior ROP and zone 1 ROP developing,[1,2] and therefore are more likely to receive IVB therapy, a treatment that is considered to have ocular benefits in treating aggressive posterior ROP and zone 1 ROP.[8] Given the differences in

Table 2. Characteristics of Comparative Studies Regarding the Neurodevelopmental Outcomes of Infants with Retinopathy of Prematurity Who Underwent Bevacizumab Treatment

| Source | Country | Study Population | Intravitreal Bevacizumab Group* | | Intravitreal Bevacizumab Dose (mg) | Treatment(s) | Control(s) | Method(s) for Neurodevelopmental Impairment Evaluation | Age at Most Recent Neurodevelopmental Impairment Evaluation |
|---|---|---|---|---|---|---|---|---|---|
| | | | *Gestational Age (wks)* | *Birth Weight (g)* | | | | | |
| Studies included in the final analysis | | | | | | | | | |
| Araz-Ersan et al,[18] 2015 | Turkey | Preterm infants treated with IVB and matched controls | 27.3 | 1017 | NA | IVB + laser | Laser | BSID-III | 2 yrs |
| Morin et al,[19] 2016 | Canada | Preterm infants (GA < 29 wks) with treated ROP | 24.9 | 739 | NA | IVB | Laser | BSID-III, GMFCS | 18 mos |
| Kennedy et al,[20] 2018 | United States | Participants of BEAT-ROP trial in a single center (GA < 27 wks) | 25.0 | 678 | 0.625 | IVB | Laser | BSID-III, GMFCS | More than 18 mos (median, 21.2 and 19.1 mos) |
| Chang et al.,[21] 2019 | Taiwan | Screened preterm infants with ROP | 24.5 | 653 | 0.625 | IVB | ROP w/o treatment | BSID-II or BSID-III | 2 yrs |
| Fan et al,[22] 2019 | Taiwan | Screened preterm infants | 26.4 | 833 | 0.625 | IVB | 1. ROP w/o treatment†<br>2. No ROP | BSID-III | 1–3 yrs (mean, 1.49 yrs) |
| Natarajan et al,[23] 2019 | United States | Extremely preterm infants (GA < 27 wks) with ROP | 24.4 | 630 | NA | IVB | Laser and/or cryotherapy | BSID-III, GMFCS | 18–22 mos or 22–26 mos (median, 23 mos) |
| Raghuram et al,[24] 2019 | Canada | Preterm infants treated for ROP | 24.4 | 722 | 0.625 | IVB | Laser | BSID-III/ASQ, GMFCS | 18–24 mos |
| Rodriguez et al,[25] 2019 | United States | Preterm infants treated for ROP | 24.7 | 665 | NA | IVB (+ deferred laser) | Laser | BSID-III, GMA | 2 yrs |
| Studies excluded from the final analysis | | | | | | | | | |
| Lien et al,[16] 2016 | Taiwan | ELBW infants treated for ROP | 25.0 | 750 | 0.625 | 1. IVB only<br>2. IVB + laser | Laser | BSID-II | 24 mos |
| Chen et al,[17] 2018 | United States | Preterm infants treated for ROP | 25.0 | 622 | 0.625 | IVB | Laser | BSID-III, Capute scales | Mean, 20.4 mos |

ASQ = Ages and Stages Questionnaire; BEAT-ROP = Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity; BSID = Bayley Scales of Infant and Toddler Development; ELBW = extremely low birth weight; GA = gestational age; GMA = General Movement Assessment; GMFCS = Gross Motor Function Classification System; IVB = intravitreal bevacizumab; NA = not available; ROP = retinopathy of prematurity; w/o = without.

*The mean GA and mean BW of the IVB group are presented. Two studies[21,23] reported the median and interquartile ranges, and the results have been converted to means based on the method proposed by Wan et al.[28]

†Only ROP patients who had not received treatment were included in the meta-analysis as controls; screened preterm infants without ROP were excluded.

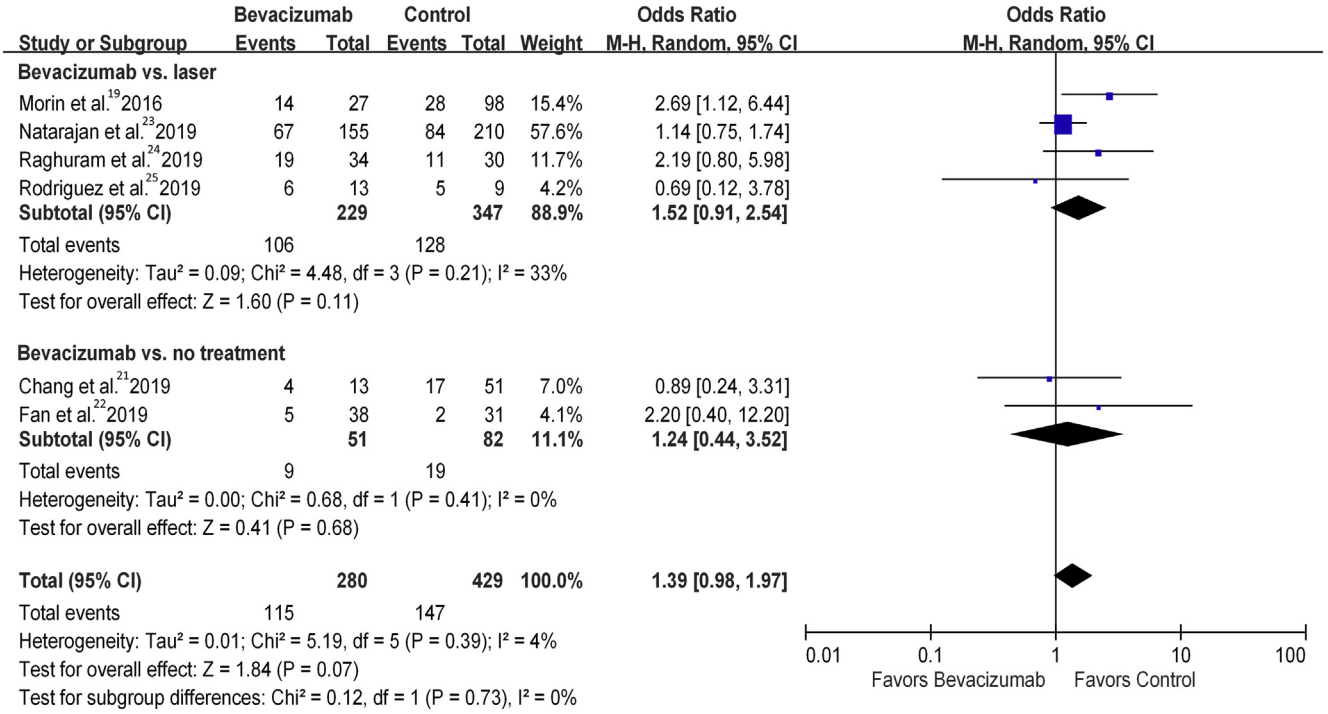


**Figure 2.** Odds ratio for severe neurodevelopmental impairment in infants treated with intravitreal bevacizumab compared with control participants. Control groups included infants with retinopathy of prematurity (ROP) treated with laser and ROP infants without treatment. CI = confidence interval; M-H = Mantel-Haenszel.

the incidence of NDI and severity of ROP in infants born with varying degrees of prematurity, as well as their different degrees of organ maturation, GA and birth weight should be included as potential confounding factors when evaluating the developmental outcomes in infants who have undergone IVB treatments. The variation in patient populations among included studies, such as including only patients with small GA[19,20,23] or including all patients with treated ROP,[21,22,24,25] may lead to a difference in average GA or birth weight. Nonetheless, we found no difference in any of the subgroup comparisons stratified based on the aforementioned differences. The results of the post hoc subgroup analysis might be confounded by the potential overlap of GA and birth weight in the IVB group among different studies, thus causing misclassification bias. This was supported by the fact that 3 studies[21,24,25] that enrolled all treated patients had similar average GA and birth weight in the IVB group compared with the 3 studies[19,20,23] that included only infants with low GA. However, most studies included in our meta-analysis did not report subgroup results based on GA or birth weight. In addition, we did not have full access to the original data of all studies, thus impeding us from concluding definitively whether the effect of IVB on the developmental outcomes was correlated with GA and birth weight. Further studies are required to clarify if IVB has different effects on infants born with varying degrees of immaturity.

One major concern in all the analyzed studies is selection bias. Only in 1 study[20] were the two treatments, IVB or laser, assigned randomly. In the study by Morin et al,[19] the infants who received IVB showed relatively poor Score for Neonatal Acute Physiology, second generation (SNAP-II) scores; these scores indicated more severe systemic illness at birth. Another study that reported inferior outcomes in its IVB group observed lower birth weight as well as prolonged ventilatory and oxygen support in infants who had undergone IVB treatment.[23] Even in studies that reported no differences in neurodevelopmental outcomes, IVB often was assigned to patients whose conditions were relatively severe and who were unable to tolerate long-term general anesthesia or sedation for laser treatment.[24] In addition, the two studies[21,22] that compared ROP infants with and without treatment had clear baseline differences in terms of GA, birth weight, and period of respiratory support, all of which are factors associated with an increased risk of NDI.[44–46] However, these baseline differences, which favored the control group, did not result in an increased risk of sNDI in the IVB group in our analysis; this finding further supports that IVB treatment does not significantly affect the outcomes of sNDI.

Another limitation of the present study is the small number of analyzed studies. We observed no publication bias among the 8 included studies (Fig S5, available at www.aaojournal.org). Two comparative studies were identified but were excluded from our analysis owing to a lack of detailed data on outcomes of interest[17] and because they had used an older version of the Bayley scales (the second edition) for outcome evaluations.[16]

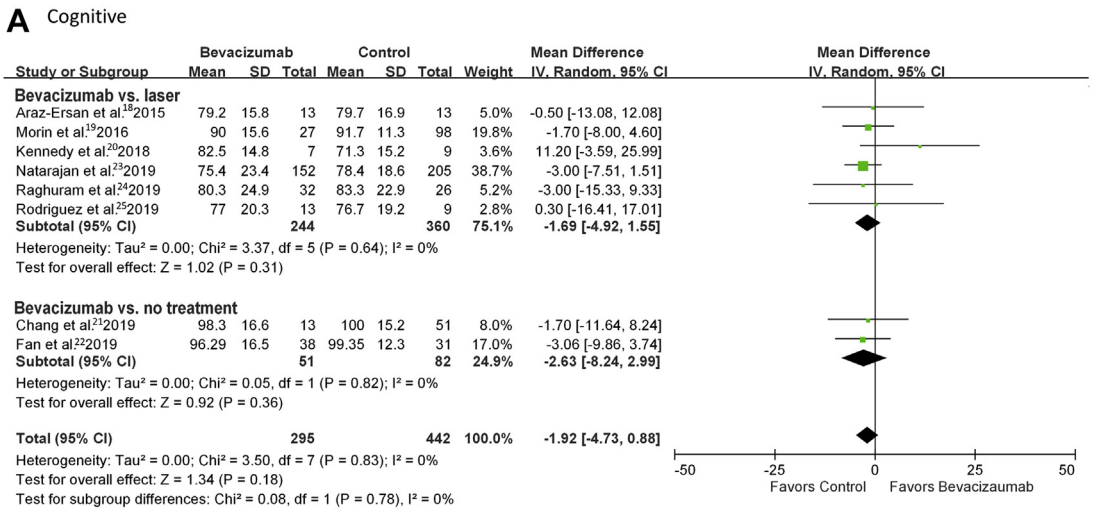


**Figure 3.** Mean differences in multiple domains of Bayley Scales of Infant and Toddler Development, Third Edition, scores between infants treated with intravitreal bevacizumab and control participants. Control groups included infants with retinopathy of prematurity (ROP) treated with laser and ROP infants without treatment. **A**, Mean difference in cognitive function scores. **B**, Mean difference in language scores. **C**, Mean difference in motor scores. CI = confidence interval; IV = inverse variance; SD = standard deviation.

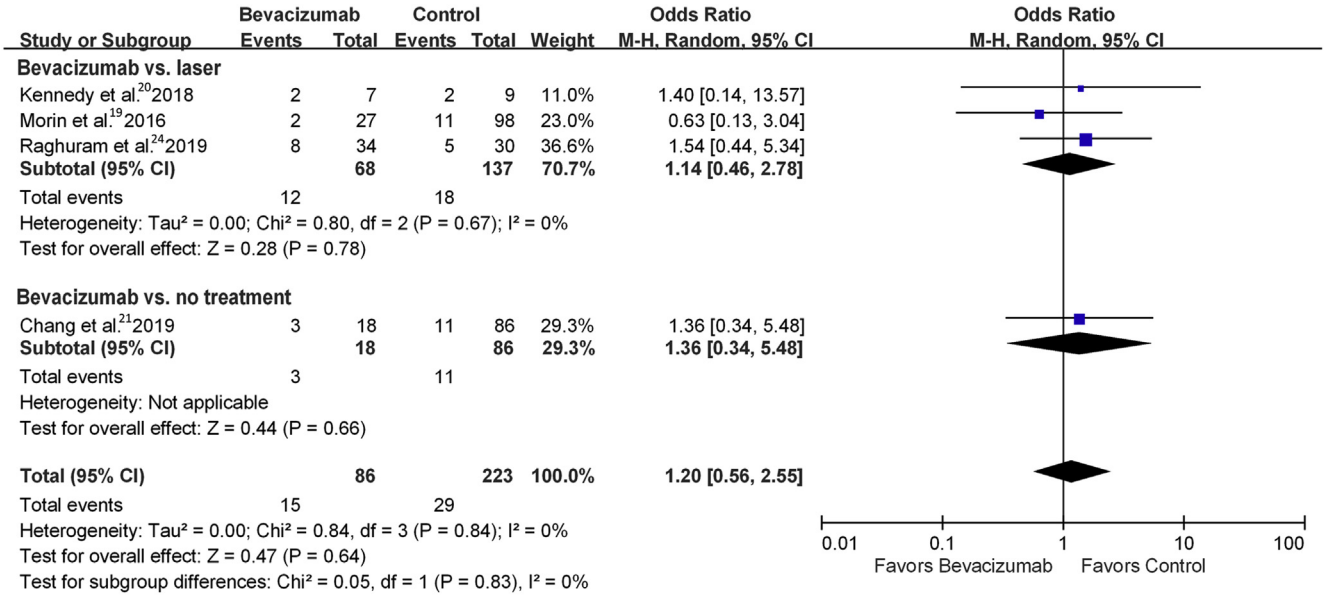


**Figure 4.** Odds ratio for cerebral palsy in infants treated with intravitreal bevacizumab compared with control participants. Control groups included infants with retinopathy of prematurity (ROP) treated with laser and ROP infants without treatment. CI = confidence interval; M-H = Mantel-Haenszel.

Nevertheless, those two studies both revealed no differences in developmental outcomes between laser- and IVB-treated infants. Another study that reported the 5-year outcomes of 13 IVB-treated patients without a control group found only 1 infant with neurodevelopmental delay; however, this finding might have resulted from pre-existing pulmonary dysplasia or intraventricular hemorrhage.[15] In addition, during our literature search, we found 6 unpublished meeting abstracts[47–52] that reported on neurodevelopmental outcomes after IVB. All 6, which were reports of comparative studies, observed no differences in neurodevelopmental outcomes between the IVB and control groups. Although it was not included in the current analysis, all the aforementioned evidence is likely to support our conclusion.

The results of Grades of Recommendation, Assessment, Development, and Evaluation in our study suggested a generally low quality of evidence from current literature, likely because of the inclusion of only observational studies and no RCTs. The study by Kennedy et al,[20] which included 11% (16 of 150) of the infants enrolled in the BEAT-ROP study, was considered to have the lowest risk of bias among all included studies; however, it had too few patients to have a major impact on the results of the meta-analysis. Although their results of Bayley III composition scores and incidence of CP were in line with our findings, their study did not report on the incidence of either NDI or sNDI. Although the other included studies generally had a low risk of bias (7 to 9 stars in the Newcastle-Ottawa Scale; Table S3), they also had limitations, including potential bias in the selection and representativeness of the cohort,[18–20] comparability between the study and control groups,[21,22,25] and adequacy of follow-up.[18,24,25] A properly designed RCT can minimize the aforementioned biases and strengthen the quality of evidence. Using randomly assigned treatment groups and a long-term follow-up with complete neurodevelopmental evaluation performed by pediatricians blinded to the assigned treatment can provide high-quality evidence. Therefore, to confirm our findings, we recommend a follow-up study of the participants in the BEAT-ROP trial[5] or a new RCT to address neurodevelopmental outcomes in preterm infants with ROP who received IVB treatment.

The present study has several other limitations. First, the definition of sNDI differed slightly among the analyzed studies; specifically, the presence of visual impairment and CP incidence were not included consistently as a criterion of sNDI. This factor also may explain the major differences in sNDI incidence in the analyzed studies. Second, 4 of the included studies[18,19,23,25] did not report bevacizumab dosage. The suppression of systemic VEGF by IVB was reported to be dose dependent.[30,32] In addition, several studies[53–55] found that low concentrations of IVB were still effective for treating ROP. Hence, the effect of IVB on neurodevelopment may differ from that observed in our study if the dosage is lowered. Studying long-term neurodevelopmental outcomes of infants treated with varying concentrations of IVB could provide valuable information regarding its dose-dependent effect on NDI, leading to stronger evidence. Third, other anti-VEGF drugs, including ranibizumab[56] and aflibercept,[57] also are effective in treating type 1 ROP. The results from a recent RCT, the Ranibizumab Compared with Laser Therapy for the Treatment of Infants Born Prematurely with Retinopathy of Prematurity study,[56] suggested that 0.2 mg ranibizumab may be superior to laser therapy in treating ROP, along with limited systemic VEGF suppression. These findings, as well as those of the ongoing Aflibercept for Retinopathy of Prematurity—Intravitreal Injection versus Laser Therapy and Intravitreal Aflibercept Compared to Laser Photocoagulation in Patients with Retinopathy of Prematurity studies, may

Table 5. Quality of Evidence and Summary of Findings

| No. of Participants (Studies) | Study Limitations* | Consistency | Directness | Precision | Publication Bias | Relative Effect (95% Confidence Interval) | Best Estimate of Non–Intravitreal Bevacizumab Group† | Absolute Effect (95% Confidence Interval) | Quality (Grades of Recommendation, Assessment, Development, and Evaluation)‡ |
|---|---|---|---|---|---|---|---|---|---|
| Severe NDI<br>709 (6) | Only observational studies | No important inconsistency | Direct | No important imprecision | Unlikely | OR, 1.39 (0.98–1.97) | 343 per 1000 | 77 more per 1000 (from 5 fewer to 164 more) in the IVB group | ⊕⊕◯◯<br>Low |
| Bayley-III, Cognitive<br>737 (8) | Only observational studies | No important inconsistency | Direct | No important imprecision | Unlikely | NA | 85.46 | The cognitive score was 1.92 points worse (4.73 worse to 0.88 better) in the IVB group | ⊕⊕◯◯<br>Low |
| Bayley-III, Language<br>727 (8) | Only observational studies | No important inconsistency | Direct | No important imprecision | Unlikely | NA | 82.15 | The language score was 1.32 points worse (4.63 worse to 1.99 better) in the IVB group | ⊕⊕◯◯<br>Low |
| Bayley-III, Motor<br>725 (8) | Only observational studies | No important inconsistency | Direct | No important imprecision | Unlikely | NA | 80.86 | The motor score was 3.66 points worse (6.79–0.54 worse) in the IVB group | ⊕⊕◯◯<br>Low |
| Cerebral palsy<br>309 (4) | Only observational studies | No important inconsistency | Direct | Imprecision (−1)§ | Unlikely | OR, 1.20 (0.56–2.55) | 130 per 1000 | 22 more per 1000 (from 53 fewer to 146 more) in the IVB group | ⊕◯◯◯<br>Very low |

IVB = intravitreal bevacizumab; NA = not applicable; NDI = neurodevelopmental impairment; OR = odds ratio.
*Observational studies start with low quality in the Grades of Recommendation, Assessment, Development, and Evaluation system.
†Includes laser-treated patients and patients with retinopathy of prematurity, but without treatment.
‡Grades of Recommendation, Assessment, Development, and Evaluation system was applied according to Guyatt et al.[29]
§The relatively small number of included patients and the events led to imprecision in the outcome of cerebral palsy and a 1-step downgrade in Grades of Recommendation, Assessment, Development, and Evaluation.

change the drug of choice for ROP when anti-VEGF therapy is indicated. However, the effects of these drugs on systemic VEGF suppression differ from those of bevacizumab,[9,58] and their effect on long-term development remains unknown. Several ongoing trials are evaluating the long-term neurodevelopmental outcomes after anti-VEGF treatment in patients with ROP, including infants receiving ranibizumab (Comparing Alternative Ranibizumab Dosages for Safety and Efficacy in Retinopathy of Prematurity [clinicaltrials.gov identifier, NCT02134457], Rainbow Extension Study [clinicaltrials.gov identifier, NCT02640664]) and aflibercept (extension study of Aflibercept for Retinopathy of Prematurity—Intravitreal Injection Versus Laser Therapy [clinicaltrials.gov identifier, NCT04015180] and extension study of Intravitreal Aflibercept Compared to Laser Photocoagulation in Patients with Retinopathy of Prematurity [clinicaltrials.gov identifier, NCT04515524]) treatments. These forthcoming results in the next few years may help us to understand better the effects of systemic VEGF suppression on the neurodevelopmental outcomes in prematurity.

In conclusion, our results suggest that in ROP patients, IVB treatment does not significantly increase the risks of sNDI and CP and results in similar cognitive and language performance as that of control participants. A minor difference in the motor scores of Bayley III after IVB treatment was noted; however, the clinical significance of this difference is unclear. In addition, the overall quality of evidence was low because of the lack of results from RCTs. Intravitreal bevacizumab appeals to ocular benefits and could be used as an alternative first-line treatment for selective conditions in ROP, and our findings indicate that sNDI is not likely a result of IVB and that therapeutic equipoise exists. Thus, the setting is appropriate to conduct an RCT. Therefore, we suggest that the long-term developmental outcomes of the BEAT-ROP study be evaluated and that further RCTs are required to better understand the systemic safety of IVB in treating ROP. Finally, we suggest that until high-quality evidence has been established, clinicians carefully should weigh the benefits and risks of IVB treatment before treating infants with ROP.

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## Footnotes and Disclosures

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No animal subjects were included in this study.

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Abbreviations and Acronyms:
**Bayley III** = Bayley Scales of Infant and Toddler Development, Third Edition; **BEAT-ROP** = Bevacizumab Eliminates the Angiogenic Threat of ROP; **CI** = confidence interval; **CP** = cerebral palsy; **GA** = gestational age; **IVB** = intravitreal bevacizumab; **MD** = mean difference; **NDI** = neurodevelopmental impairment; **OR** = odds ratio; **RCT** = randomized controlled trial; **ROP** = retinopathy of prematurity; **SD** = standard deviation; **SNAP-II** = Score for Neonatal Acute Physiology, second generation; **sNDI** = severe neurodevelopmental impairment; **VEGF** = vascular endothelial growth factor.

Key Words:
Retinopathy of prematurity, neurodevelopmental impairment, bevacizumab, vascular endothelial growth factor, Meta-Analysis.

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