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Correspondence: Kathleen A. Kennedy, MD, MPH, Department of Pediatrics, McGovern Medical School at UTHealth, 6431 Fannin, Suite 2.106, Houston, TX 77030 (Kathleen.A.Kennedy@uth.tmc.edu).

*A complete listing of the BEAT-ROP Cooperative Group is provided as eSupplement 1 (available at jaapos.org).

Members of the BEAT-ROP Cooperative Group:

Principal Investigator: Helen A. Mintz-Hittner, M.D., the University of Texas Health Science Center at Houston-Medical School, Memorial Hermann Medical Plaza, 6400 Fannin St., Suite1800, Houston, TX 77030, e-mail: Helen.A.Mintz-Hittner@uth.tmc.edu. Hospitals/Centers, Investigators, and Clinical Coordinators: 1) Huntington Memorial Hospital, Pasadena, CA: Ricardo L. Liberman, M.D. (neonatologist) and Khaled A. Tawansy, M.D. (vitreo-retinal surgeon) (co-investigators); 2) Presbyterian-St. Luke's Hospital, Rocky Mountain Hospital for Children, Denver, CO: Delphine M. Eichorst, M.D. (neonatologist), Robert A. King, M.D. (pediatric ophthalmologist) and Christopher Bardorf, M.D. (pediatric ophthalmologist) (co-investigators); Melissa Rutt, R.N., B.S.N. (clinical coordinator); 3) Children's Hospital of Illinois, OSF St. Francis Medical Center: James R. Hocker, M.D. (neonatologist), Steven J. Lichtenstein, M.D. (pediatric ophthalmologist) and Parashos A. Lagouros, M.D. (vitreo-retinal surgeon) (coinvestigators); Julie A. Hodges, R.N.C., B.S.N. (clinical coordinator); 4) Palmetto Health Baptist Hospital, Columbia, SC: Sharon S. Ellis, M.D. (neonatologist) and W. Lloyd Clark, M.D. (vitreo-retinal surgeon) (co-investigators); Sharon Emory, R.N. (clinical coordinator); 5) Palmetto Health Richland Hospital, Columbia, SC: Victor N. Iskersky, M.D. (neonatologist) and W. Lloyd Clark, M.D. (vitreo-retinal surgeon) (co-investigators); Sharon Emory, R.N. (clinical coordinator); 6) Driscoll Children's Hospital, Corpus Christi, TX: Patricia L. Ramsay, M.D., Ph.D. (neonatologist) and Helen A. Mintz-Hittner, M.D. (pediatric ophthalmologist) (co-investigators); Kathy S. Sanchez, R.N. (clinical coordinator); 7) Baylor University Medical Center, Dallas, TX: Craig T. Shoemaker, M.D. (neonatologist) and Rand W. B. Spencer, M.D. (vitreo-retinal surgeon) (coinvestigators); Rachel Ross, R.N., M.S.N. (clinical coordinator); 8) Del Sol Medical Center, El Paso, TX: Enrique N. Ponte, M.D. (neonatologist) and Helen A. Mintz-Hittner, M.D. (pediatric ophthalmologist) (co-investigators); Michael A. Lason, R.N., N.N.P.-B.C. (clinical coordinator); 9) Las Palmas Medical Center, El Paso, TX: Luis A. Ayo, M.D. (neonatologist) and Helen A. Mintz-Hittner, M.D. (pediatric ophthalmologist) (co-investigators); Sandra C. Dieguez (clinical coordinator); 10) R.E. Thomason Hospital, the University of Texas Health Science Center at El Paso-Medical School, El Paso, TX: Garrett S. Levin, M.D. (neonatologist) and Violeta Radenovich, M.D., M.P.H. (pediatric ophthalmologist) (co-investigators); Leticia Guerra, R.N. (clinical coordinator); 11) Cook Children's Medical Center, Fort Worth, TX: David M. Riley, M.D. (neonatologist), Michael G. Hunt, M.D. (pediatric ophthalmologist), E. Alan Packwood, M.D. (pediatric ophthalmologist), and Alan A. Norman, M.D. (pediatric ophthalmologist) (co-investigators); Melinda Meacham, R.N., M.S.N., C.C.R.C. (clinical coordinator); 12) Children's Memorial Hermann Hospital, the University of Texas Health Science Center at Houston-Medical School, Houston, TX: Sophia Tsakiri, M.D. (neonatologist) and Helen A. Mintz-Hittner, M.D. (pediatric ophthalmologist) (co-investigators); De'Ann Pulido, R.N. (clinical coordinator); 13) Memorial Hermann Southwest Hospital, the University of Texas Health Science Center at Houston-Medical School, Houston, TX: Syed Hassan Haider, M.D. (neonatologist) and Helen A. Mintz-Hittner, M.D. (pediatric ophthalmologist) (co-investigators); Linda Wernecke, R.N. (clinical coordinator); 14) St. Joseph Medical Center, Houston, TX: Elizabeth O'Donnell, M.D. (neonatologist) and Helen A. Mintz-Hittner, M.D. (pediatric ophthalmologist) (co-investigators); Maria Mares (clinical coordinator); 15) Clear Lake Regional Medical Center, Webster, TX: Harvinder S. Bedi, M.D. (neonatologist) and Helen A. Mintz-Hittner, M.D. (pediatric ophthalmologist) (co-investigators); Leah M. Best, R.N., N.N.P.-B.C., Ph.D. (clinical coordinator).

Confirming Ophthalmologist: Ronan E. O'Malley, M.D. (vitreo-retinal surgeon), Houston, TX.

Compounding Pharmacist: Kenneth L. Hughes, R.Ph., Greenpark Compounding Pharmacy, Houston, TX.

Research Assistants: Cary Warner, Clinical Research Unit at Memorial Hermann Hospital, Houston, TX; Research Assistant: Maria Mares, Houston, TX; Research Assistant: Linda M. Rhodes, Houston TX; Research Assistant: Susan M. Hittner, B.B.A., M.B.A., Houston, TX; Technical Assistant: Kimberly A. Mankiewicz, Ph.D.

Members of the Planning Committee:

Helen A. Mintz-Hittner, M.D., Department of Ophthalmology and Visual Science, the University of Texas Health Science Center at Houston-Medical School: Principal Investigator of the BEAT-ROP Clinical Trial, Sponsor of the BEATROP Clinical Trial (obtained the BEAT-ROP FDA IND, listed the BEAT-ROP Clinical Trial on Clinicaltrials.gov, and provided funding from Alfred W. Lasher III Professorship research funds) and Pediatric Ophthalmologist Co-PI at the Children's Memorial Hermann Hospital; Kathleen A. Kennedy, M.D., M.P.H., Department of Pediatrics, the University of Texas Health Science Center at Houston-Medical School: Study Coordinator and Randomizer; and Sophia Tsakiri, M.D., Department of Pediatrics, the University of Texas Health Science Center at Houston-Medical School: Neonatologist Co-PI at the Children's Memorial Hermann Hospital.

Members of the Executive Committee:

All participating ophthalmologists: (in alphabetical order): Christopher Bardorf, M.D. (pediatric ophthalmologist); W. Lloyd Clark, M.D. (vitreoretinal surgeon), Michael G. Hunt, M.D. (pediatric ophthalmologist), Robert A. King, M.D. (pediatric ophthalmologist), Parashos A. Lagouros, M.D. (vitreo-retinal surgeon), Steven J. Lichtenstein, M.D. (pediatric ophthalmologist); Helen A. Mintz-Hittner, M.D. (pediatric ophthalmologist), Alan A. Norman, M.D. (pediatric ophthalmologist), E. Alan Packwood, M.D. (pediatric ophthalmologist), Ronan E. O'Malley, M.D. (vitreo-retinal surgeon); Violeta Radenovich, M.D., M.P.H. (pediatric ophthalmologist), Rand W. B. Spencer, M.D. (vitreo-retinal surgeon), and Khaled A. Tawansy, M.D. (vitreo-retinal surgeon).

Members of the BEAT-ROP Reading Center:

Medical and developmental outcomes of bevacizumab versus laser for retinopathy of prematurity

Kathleen A. Kennedy, MD, MPH[a], **Helen A. Mintz-Hittner, MD**[b], and **for the BEAT-ROP Cooperative Group**[*]

[a]Department of Pediatrics, McGovern Medical School at The University of Texas Health Science Center at Houston

[b]Department of Ophthalmology and Visual Science, McGovern Medical School at The University of Texas Health Science Center at Houston

Abstract

Background—Infants with stage 3+ retinopathy of prematurity (ROP) in zone I or zone II posterior were randomized to initial treatment with bevacizumab or laser in a multicenter trial (BEAT-ROP). The purpose of this study was to assess the effects of bevacizumab on nonophthalmologic outcomes.

Methods—At one study site, inborn infants of <27 weeks' gestational age underwent medical and standardized neurologic and developmental assessments at 18–22 months' corrected age (age after expected date of full-term delivery).

Results—Of the 18 infants enrolled at our site, 16 (7 bevacizumab, 9 laser) were evaluated for medical and neurodevelopmental outcomes at 18–28 months' corrected age. For each of the groups, the medians and ranges of growth percentiles were low compared with norms for healthy infants. The ranges for Bayley III developmental scores were also low relative to expected norms for healthy infants. There were no significant differences between the bevacizumab and laser therapy groups in weight (median percentile: bevacizumab, 18; laser, 7), length, head circumference, cerebral palsy, or Bayley scores (median Cognitive Composite Score: bevacizumab, 85; laser, 65). There was a significant difference in length of hospital stay (median days, 98 vs 140 days) favoring the bevacizumab group.

Conclusions—In this patient cohort 2-year follow-up evaluation of infants treated with bevacizumab versus laser therapy for retinopathy of prematurity showed no adverse effects on medical or neurodevelopmental outcomes.

Cryotherapy became established as routine treatment for retinopathy of prematurity (ROP) in the 1980s and was effectively replaced by laser treatment in the 1990s.[1–4] Although

Established at the World ROP Congress 2009, New Delhi, India, November 21st–23rd, 2009: Michael F. Chiang, M.D., Harkness Eye Institute, Columbia University, New York, NY, USA; Michael Shapiro, M.D, University of Illinois, College of Medicine, Chicago, IL, USA; Susana M. Teixeira, M.D., Lisbon, Portugal; Anand Vinekar, M.D., Bangalore, India.; Parag K. Shah, M.D., Tamil Nadu, India; Alay S. Banker, M.D., Ahmedabad, India.

Members of the BEAT-ROP Data and Safety Monitoring Board: Jon E. Tyson, M.D., M.P.H., the University of Texas Health Science Center at Houston-Medical School (Chairman); Robert E. Lasky, Ph.D., the University of Texas Health Science Center at Houston-Medical School (Statistician); Ms. Paula L. Knudson, the University of Texas Health Science Center at Houston-Medical School (Ethicist); Keith A. Bourgeois, M.D., (Vitreo-retinal surgeon-private practice); and Frank L. Kretzer, Ph.D., Baylor College of Medicine (Teaching and ROP research).

ablative therapy has been shown in a multicenter randomized trial to improve structural and functional outcomes, it also destroys retinal tissue, and some treated infants have poor visual outcomes.[5,6] Antivascular endothelial growth factor (VEGF) agents have been proposed as a less destructive treatment alternative. In the Bevacizimab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) trial, the first multicenter randomized trial of an anti-VEGF agent for ROP, intravitreal bevacizumab, compared to laser therapy, reduced the rate of recurrence of zone I ROP[7,8] and decreased myopia and high myopia.[9]

Since the BEAT-ROP randomized trial was published, numerous reviewers have raised concerns about the safety of bevacizumab in preterm infants.[4,10–13] Several investigators have reported that anti-VEGF antibodies can be identified systemically after intravitreal treatment.[14–16] These observations have raised concerns about the effect of anti-VEGF agents on other developing organs, particularly the lungs and the brain, of preterm infants. Recent systematic reviews[17,18] of anti-VEGF treatment for ROP have recommended that neonates be followed at least 18–24 months for visual and neurodevelopmental outcomes.[17] One large multicenter observational study from the Canadian Neonatal Network reported worse medical outcomes among infants treated with bevacizumab as compared to laser treatment.[19] However, because infants were not randomized this study is subject to selection bias; sicker infants may be preferentially treated with bevacizumab because treatment does not require transport to the operating room or intubation. Smaller observational studies have not confirmed this association.[20,21] The results of only 4 randomized trials of anti-VEGF agents for ROP (with randomization of infants rather than eyes) have been published, [7,15,22,23] and none has included medical outcomes after hospital discharge. This study investigated medical and neurodevelopmental outcomes of infants enrolled in the BEAT-ROP trial at one Houston site, where very preterm (< 27 weeks gestation at birth) inborn infants are routinely seen at 18–22 months' corrected age for medical and neurodevelopmental evaluations.

Subjects and Methods

Details of the design for this multicenter randomized trial have been previously published.[7] The study was approved by the Institutional Review Board at the University of Texas Health Science Center and registered in ClinicalTrials.gov (NCT00622726). Infants were screened for ROP according to the recommendations of the American Academy of Ophthalmology, the American Academy of Pediatrics, and the American Association for Pediatric Ophthalmology and Strabismus.[24] Infants were enrolled from March 2008 through April 2010. Infants with stage 3+ ROP in zone I or zone II posterior in both eyes were eligible for enrollment. Eligible consented infants were randomized to intravitreal bevacizumab monotherapy (0.625 mg in 0.025 ml of solution) or conventional laser therapy of both eyes. Randomization was stratified by zone I vs zone II ROP (not stratified by center). Once the primary investigator (HAM-H) determined subject eligibility and consent was obtained, infants were randomized by another investigator (KAK) who had prepared the permuted block randomization schedule and was not involved in determining eligibility or seeking consent. Caregivers were not masked. The primary outcome was recurrent ROP. Infants enrolled at the University of Texas Health Science Center at Houston site were scheduled for routine medical and neurodevelopmental follow-visits at 18–22 months' corrected age if

they were inborn and <27 weeks gestation at birth. Follow-up of infants enrolled at this site was planned as a secondary outcome; this was the only participating site with routine neurodevelopmental follow-up in place for these infants. Inpatient medical outcomes were prospectively extracted from the medical record by trained research nurses using standard definitions and are reported for all infants enrolled at this site. Intraventricular hemorrhage was graded by Papile criteria.[25] Necrotizing enterocolitis was defined as ≥ Bell's stage II.[26] Spontaneous intestinal perforation was defined as bowel perforation without evidence of necrotizing enterocolitis. Bronchopulmonary dysplasia was defined as receiving supplemental oxygen at 36 weeks' postmenstrual age. Late-onset sepsis was defined as positive blood culture for bacteria or fungi after 72 hours of age and treatment with antibiotics for ≥5 days.

Follow-up visits were scheduled as soon as feasible after 18 months' corrected age; infants were administered the Bayley Scales of Infant and Toddler Development III.[27] Infants who were too severely affected to complete the testing were assigned, by convention, a 54 for the cognitive score and a 46 for the language and motor scores. Standardized neurologic examinations were performed by certified examiners.[28] Follow-up examiners were not specifically masked to group assignment; these clinicians were not involved in the care of the infants during the acute hospitalization phase; thus, they would not have been aware of group assignment unless it was mentioned by the parents in the course of the infant's post-discharge care. Gross motor performance was categorized from 0 (normal) to 5 (most impaired), using the modified Gross Motor Function Classification System.[29] Cerebral palsy was defined as moderate-severe with abnormal muscle tone in at least one extremity that was associated with abnormal control of movement or posture and a gross motor function score of at least 2.[30] Other outcomes included growth as assessed by height, weight and fronto-occipital circumference. Centers for Disease Control growth charts[31] were used to calculate percentiles for growth based on corrected age.

Data analysis was performed using Stata version 14 (StataCorp, College Station, TX). Descriptive statistics were used to summarize baseline characteristics. Categorical outcomes were compared using the Fisher exact test. The Wilcoxon rank-sum test was used to assess differences in continuous variable outcomes by group, because the distributions were skewed. Minitab 12.2 (Minitab Inc, State College, PA) was used to calculate confidence intervals for differences in medians. Systemic complications of prematurity that occurred predominantly prior to enrollment in BEAT-ROP were not compared statistically.

Results

Of the 150 infants enrolled in the BEAT-ROP multicenter trial, 18 were enrolled at the University of Texas Health Science Center at Houston. All survived to hospital discharge. One infant was not eligible for follow-up and 1 died after discharge at 29 months of age (neurodevelopmental assessment not performed). The remaining 16 infants (7 bevacizumab, 9 laser) were evaluated between 18 and 28 months' corrected age (eFigure 1).

Baseline demographic and clinical characteristics for all enrolled infants are given in Table 1 and compared to baseline demographic and clinical characteristics for the BEAT-ROP

cohort. Characteristics at birth were reasonably well balanced, but the point estimates for mean birth weight and gestational age favored the bevacizumab group. In-hospital medical outcomes are provided in Table 2. Most of the important in-hospital complications of prematurity occurred before the typical age of enrollment in BEAT-ROP (postmenstrual age of 35 weeks). There was no difference in survival to discharge or discharge on oxygen between the bevacizumab and laser groups. The length of hospital stay was significantly shorter in the bevacizumab group ($P = 0.03$).

Baseline demographic and clinical characteristics for the infants seen in follow-up are provided in Table 3. After the loss of 1 infant in each group, the birth weight and gestational age differences between groups were smaller. Follow-up outcomes are provided in Table 4. There were no significant differences between bevacizumab and laser groups in percentiles for weight, length, or head circumferences, and the medians and ranges were similar between groups. Poor growth, as evidenced by low median percentiles, was common in each group. Only 1 infant, in the bevacizumab group, was still receiving supplemental oxygen at the time of follow-up. There were no significant differences between groups in motor scores, cerebral palsy, or Bayley scores. The medians for Bayley scores were all <100 for each group, and the point estimates favored the bevacizumab group. None of the infants in this sample was assigned a low score because of severe impairment.

Discussion

In this single-site study of outcomes in infants enrolled in a randomized trial of bevacizumab versus laser treatment for ROP, we found no adverse effects of bevacizumab treatment. The observed difference in length of stay favoring the bevacizumab group is likely explained by differences in baseline characteristics, although it could also be explained by prolongation of hospital stay after intubation and anesthesia for laser therapy. This differs from the findings of an observational study that reported worse outcomes for infants treated with bevacizumab compared to laser.[19] There are two potential explanations for this difference. First, our patients were randomized to bevacizumab versus laser; therefore, there was no systematic difference between patients who received one treatment versus the other. In a nonrandomized observational study, where treatment is chosen based on clinician preference, there is an opportunity for higher risk infants to preferentially receive one treatment versus the other. In the case of a decision between bevacizumab and laser treatment, it is plausible that sicker infants would preferentially be treated with bevacizumab to avoid the need for transport to the operating room and general anesthesia with mechanical ventilation. Second, the observational study was much larger (125 infants) and thus had greater power to identify differences. Although we did not identify any concerning trends toward worse outcomes among infants treated with bevacizumab, we acknowledge that our study was not adequately powered to identify small but clinically important differences. On the other hand, the single-center follow-up allowed for routine inclusion of all infants eligible for the site's established follow-up program; thus, there was no bias in selection of the subsample of BEAT-ROP infants included in this study. Houston is an ethnically and racially mixed neonatal intensive care unit population, but there may be demographic differences between our site and other BEAT-ROP study sites. As other studies have shown, this group of infants who met treatment criteria for ROP was a high-risk subgroup group of

premature infants with relatively high rates of other neonatal complications, putting them at high risk of adverse follow-up outcomes.[32,33] Thus it is not surprising that growth and neurodevelopmental outcomes were not as good as outcomes reported for less selected groups of premature infants.[34,35] For those concerned about the systemic effects of bevacizumab on premature infants, this study should provide some reassurance that the adverse effects of bevacizumab reported in the previous large observational study were not apparent in our randomized infants.

The main strength of this study is the randomized allocation of patients. The most important limitation is the small sample size. Although the power to identify differences in our study is very low, as illustrated by the wide confidence intervals for the differences, this report represents the only report to date of neurodevelopmental outcomes for infants randomized to bevacizumab versus laser. As such, it represents the most unbiased estimate of the effect if bevacizumab on growth and neurodevelopmental outcomes. We agree with others that more data are needed regarding the long-term effects of bevacizumab and other anti-VEGF agents on premature infants. We are aware of two ongoing randomized trials of anti-VEGF agents versus laser treatment (NCT 01993043 [bevacizumab] and NCT 02375971 [ranibizumab]), although there are other studies comparing different doses or different preparations. A 5-year developmental follow-up is planned for the first of these trials; there is increasing recognition that neurodevelopmental testing at 18–24 months can overestimate severe disability and cannot detect limitations in more sophisticated domains, such as executive functioning.[36] Our hope is that follow-up will be incorporated into the planned ophthalmologic follow-up for all of these trial infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Gilbert C. Retinopathy of prematurity: a global perspective of the epidemics, population of babies at risk and implications for control. Early Hum Dev. 2008; 84:77–82. [PubMed: 18234457]
2. Kong L, Fry M, Al-Samarraie M, Gilbert C, Steinkuller PG. An update on progress and the changing epidemiology of causes of childhood blindness worldwide. J AAPOS. 2012; 16:501–7. [PubMed: 23237744]
3. Fielder A, Blencowe H, O'Connor A, Gilbert C. Impact of retinopathy of prematurity on ocular structures and visual functions. Arch Dis Child Fetal Neonatal Ed. 2015; 100:F179–F184. [PubMed: 25336678]
4. Hartnett ME. Advances in understanding and management of retinopathy of prematurity. Surv Ophthalmol. 2017; 62:257–76. [PubMed: 28012875]

5. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity: Snellen visual acuity and structural outcome at 5½ years after randomization. Arch Ophthalmol. 1996; 114:417–24. [PubMed: 8602778]

6. The Early Treatment for Retinopathy of Prematurity Cooperative Group. Grating visual acuity results in the Early Treatment for Retinopathy of Prematurity Study. Arch Ophthalmol. 2011; 129:840–46. [PubMed: 21746974]

7. Mintz-Hittner HA, Kennedy KA, Chuang AZ, BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med. 2011; 364:603–15. [PubMed: 21323540]

8. Mintz-Hittner HA, Geloneck MM, Chuang AZ. Clinical management of recurrent retinopathy of prematurity after intravitreal bevacizumab monotherapy. Ophthalmology. 2016; 123:1845–55. [PubMed: 27241619]

9. Geloneck MM, Chuang AZ, Clark WL, et al. BEAT-ROP Cooperative Group. Refractive outcomes following bevacizumab monotherapy compared with conventional laser treatment: a randomized clinical trial. JAMA Ophthalmol. 2014; 132:1327–33. [PubMed: 25103848]

10. Reynolds JD. Bevacizumab for retinopathy of prematurity. New Engl J Med. 2011; 364:677–8. [PubMed: 21323546]

11. Beharry KD, Valencia GB, Lazzaro DR, Aranda JV. Pharmacologic interventions for the prevention and treatment of retinopathy of prematurity. Semin Perinatol. 2016; 40:189–202. [PubMed: 26831641]

12. Darlow BA, Ells AL, Gilbert CE, Gole GA, Quinn GE. Are we there yet? Bevacizumab therapy for retinopathy of prematurity. Arch Dis Child Fetal Neonatal Ed. 2013; 98:F170–F174. [PubMed: 22209748]

13. Good WV. Bevacizumab for retinopathy of prematurity: treatment when pathology is embedded in a normally developing vascular system. Ophthalmology. 2016; 123:1843–4. [PubMed: 27549875]

14. Sato T, Wada K, Arahori H, et al. Serum concentrations of bevacizumab (Avastin) and vascular endothelial growth factor in infants with retinopathy of prematurity. Am J Ophthalmol. 2012; 153:327–33. [PubMed: 21930258]

15. Kong L, Bhatt AR, Demny AB, et al. Pharmacokinetics of bevacizumab and its effects on serum VEGF and IFG-1 in infants with retinopathy of prematurity. Invest Ophthalmol Vis Sci. 2015; 56:956–61. [PubMed: 25613938]

16. Wu W, Shih C, Lien R, et al. Serum vascular endothelial growth factor after bevacizumab or ranibizumab treatment for retinopathy of prematurity. Retina. 2016; 0:1–8.

17. Chawla D, Darlow B. Anti-vascular endothelial growth factor preparations in the treatment of retinopathy of prematurity: balancing risks and benefits. Indian Pediatrics. 2016; 53:S129–36. [PubMed: 27915321]

18. Sankar MJ, Sankar J, Mehta M, Bhat V, Srinivasan R. Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity. 2016. Cochrane Database Syst Rev. 2016; 2:CD009734. [PubMed: 26932750]

19. Morin J, Luu TM, Superstein R, et al. Neurodevelopmental outcomes following bevacizumab injections for retinopathy of prematurity. Pediatrics. 2016; 137:e20153218. [PubMed: 27244705]

20. Araz-Ersan B, Kir N, Tuncer S, et al. Preliminary anatomical and neurodevelopmental outcomes of intravitreal bevacizumab as adjunctive treatment for retinopathy of prematurity. Curr Eye Res. 2015; 40:585–91. [PubMed: 25025864]

21. Lien R, Yu M, Hsu K, et al. Neurodevelopmental outcomes in infants with retinopathy of prematurity and bevacizumab treatment. PLoS ONE. 2016; 11:e0148019. [PubMed: 26815000]

22. Autrata R, Krejcirova I, Senkova K, Holousova M, Dolezel Z, Borek I. Intravitreal pegaptanib combined with diode laser therapy for stage 3+ retinopathy of prematurity in zone I and posterior zone II. Eur J Ophthalmol. 2012; 22:687–94. [PubMed: 22669848]

23. Karkhaneh R, Khodabande A, Riazi-Eafahani M, et al. Efficacy of intravitreal bevacizumab for zone-II retinopathy of prematurity. Acta Ophthalmol. 2016; 94:e417–e420. [PubMed: 27009449]

24. Section of Ophthalmology American Academy of Pediatrics, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus. Screening

examination of premature infants for retinopathy of prematurity. Pediatrics. 2006; 117:572–6. [Erratum, Pediatrics 2006;118:1324.]. [PubMed: 16452383]

25. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr. 1978; 92:529–34. [PubMed: 305471]
26. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis: therapeutic decisions based upon clinical staging. Ann Surg. 1978; 187:1–7. [PubMed: 413500]
27. Bayley scales of infant and toddler development. 3rd. San Antonio, TX: Harcourt Assessment; 2006.
28. Newman JE, Bann CM, Vohr BR, Dusick AM, Higgins RD, Follow-up Group of Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Improving the Neonatal Research Network annual certification for neurologic examination of the 18–22 month child. J Pediatr. 2012; 161:1041–6. [PubMed: 22748517]
29. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol. 1997; 39:214–23. [PubMed: 9183258]
30. Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy. Devel Med Child Neurol Suppl. 2007; 109:8–14. [Erratum, Dev Med Child Neurol 2007;49:480.]. [PubMed: 17370477]
31. Centers for Disease Control and Prevention, National Center for Health Statistics. https://www.cdc.gov/growthcharts/cdc_charts.htm. Updated 12/7/16. Accessed 3/1/17
32. Schmidt B, Asztalos EV, Roberts RS, et al. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months. JAMA. 2003; 289:1124–9. [PubMed: 12622582]
33. Schmidt B, Davis PG, Asztalos EV, Solimano A, Roberts RS. Association between severe retinopathy of prematurity and nonvisual disabilities at age 5 years. JAMA. 2014; 311:523–5. [PubMed: 24496539]
34. Navarrete CT, Wrage LA, Carlo WA, et al. Growth outcomes of preterm infants exposed to different oxygen saturation target ranges from birth. J Pediatr. 2016; 176:62–8. [PubMed: 27344218]
35. Vaucher YE, Peralta-Carcelen M, Finer NN, et al. Neurodevelopmental outcomes in the early CPAP and pulse oximetry trial. New Engl J Med. 2012; 367:2495–2504. [PubMed: 23268664]
36. Hintz SR, Newman JE, Vohr BR. Changing definitions of long-term follow-up: should “long-term” be even longer? Semin Perinatol. 2016; 40:398–409. [PubMed: 27417651]

Table 1

Baseline characteristics of all infants enrolled at site

	Bevacizumab group		Laser group	
	UT Houston (n = 8)	**BEAT-ROP (n = 75)**	**UT Houston (n = 10)**	**BEAT-ROP (n = 75)**
BW, g, mean (range)	687 (600–780)	657 (430–1170)	600 (489–715)	670 (310–1310)
GA, weeks, mean (range)	25 (24 – 28)	24 (22 – 27)	24 (24 – 26)	24 (22 – 30)
Race, n (%)				
Black	2 (25)	12 (16)	2 (20)	19 (25)
White	1 (12)	13 (17)	4 (40)	15 (20)
Hispanic	5 (62)	47 (63)	4 (40)	38 (51)
Sex, male, n (%)	6 (75)	47 (63)	5 (50)	50 (67)
PNA,[a] days, mean (range)	66 (54 – 76)	75 (47 – 116)	74 (63 – 96)	72 (25 – 116)
PMA,[a] weeks, mean (range)	34.8 (31.7–36.9)	35.2 (31.1–41.6)	34.9 (33.1–37.4)	34.8 (31.1–40.0)

BW, birth weight; *GA*, gestational age; *PMA*, postmenstrual age; *PNA*, postnatal age.

[a]At BEAT-ROP enrollment.

Table 2

In-hospital medical outcomes (among all infants enrolled at site)

Outcome	Bevacizumab group (n = 8)	Laser group (n = 10)
Intracranial hemorrhage grade, n (%)[25]		
0 (none)	6 (75)	7 (70)
1 (germinal matrix only)	1 (12)	0
2 (intraventricular extravasation)	0	0
3 (ventricular dilation)	1 (12)	3 (30)
4 (intraparenchymal hemorrhage)	0	0
Necrotizing enterocolitis (≥Bell's stage 2) or spontaneous intestinal perforation, n (%)	3 (38)	4 (40)
Late - onset sepsis or meningitis, n (%)	4 (50)	5 (50)
Days mechanical ventilation, median (range)	42 (20–107)	49 (5–144)
Days continuous positive airway pressure, median (range)	24 (9–44)	36 (3–121)
Bronchopulmonary dysplasia, n (%)	6 (75)	7 (70)
Discharged on oxygen	3 (38)	4 (40)
Survived to discharge, n (%)	8 (100)	10 (100)
Length hospital stay, days, median (range)	98 (90–186)	140 (109–382)

Table 3

Baseline characteristics of infants evaluated at follow-up

Characteristic	Bevacizumab group (n = 7)	Laser group (n = 9)
Birth weight, g, mean (range)	678 (600–780)	605 (489–715)
GA, weeks, mean (range)	25.0 (23.7–26.0)	24.4 (23.4–25.7)
Race, n (%)		
Black	2 (29)	1 (11)
White	0	4 (44)
Hispanic	5 (71)	4 (44)
Sex, male, n (%)	5 (71)	5 (62)
PNA,[a] days, mean (range)	66 (54–76)	74 (63–86)
PMA,[a] weeks, mean (range)	34.5 (31.7–36.9)	35.0 (33.1–37.4)

GA, gestational age; *PMA*, postmenstrual age; *PNA*, postnatal age.

[a]At enrollment into BEAT-ROP.

Table 4

Follow-up outcomes

Outcome	Bevacizumab group (n = 7)	Laser group (n = 9)	Difference in medians (95% CI)	*P* value
	Median (range)	Median (range)		
Corrected age at follow-up, months	21.2 (18.1–28.5)	19.1 (18.0–21.4)	1.9 (−0.1 to 9.0)	0.10
Weigh t percentile for age	18 (0 – 56)	7 (0 – 39)	14 (− 7 to 49)	0.27
Length percentile for age	8 (3–83)[a]	29 (2–73)	−11 (−54 to 16)	0.39
Head circumference percentile for age	0 (0–77)[a]	8 (0–77)	−2 (−24 to 47)	0.46
Cognitive composite score	85 (60 – 100)	65 (55 – 100)	10 (− 5 to 30)	0.06
Language composite score	89 (59–91)	71 (47–106)	12 (−15 to 30)	0.18
Motor composite score	79 (58 – 100)	70 (55 – 100)[b]	8 (−15 to 33)	0.22
	No. (%)	No. (%)	RR (95% CI)	
On oxygen at follow-up	1 (14)[b]	0	NA	0.40
Gross motor function level			Normal/n 1.61 (0.67 to 3.83)	0.85
Normal	5 (71)	4 (44)		
1	0	2 (22)		
2	1 (14)	1 (11)		
3	0	1 (11)		
4	1 (14)	1 (11)		
5	0	0		
Cerebral palsy	2 (28)	2 (22)	1.29 (0.24 to 6.99)	1.00

CI, confidence interval; *RR*, relative risk.

[a] 2 missing.

[b] 1 missing.