

Intravitreal Bevacizumab for Retinopathy of Prematurity: Refractive Error Results

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- **PURPOSE:** To evaluate refractive error in infants who underwent intravitreal bevacizumab injection for treatment of threshold retinopathy of prematurity (ROP).
- **DESIGN:** Retrospective nonrandomized interventional comparative study.
- **METHODS:** The study group included all infants who consecutively received a single intravitreal bevacizumab (0.375 mg or 0.625 mg) injection for therapy of threshold ROP in fundus zone I or zone II. The control group included infants who had previously undergone retinal argon laser therapy of ROP. The follow-up examination included refractometry under cycloplegic conditions.
- **RESULTS:** The study group included 12 children (23 eyes; mean birth weight: 622 ± 153 g; gestational age: 25.2 ± 1.6 weeks) and the control group included 13 children (26 eyes; birth weight: 717 ± 197 g; gestational age: 25.3 ± 1.8 weeks). Both groups did not differ significantly in birth age and weight and follow-up. At the end of follow-up at 11.4 ± 2.3 months after birth, refractive error was less myopic in the study group than in the control group (-1.04 ± 4.24 diopters [median: 0 diopters] vs -4.41 ± 5.50 diopters [median: -5.50 diopters]; $P = .02$). Prevalence of moderate myopia ($17\% \pm 8\%$ vs $54\% \pm 10\%$; $P = .02$; OR: 0.18 [95% CI: 0.05, 0.68]) and high myopia ($9\% \pm 6\%$ vs $42\% \pm 10\%$; $P = .01$; OR: 0.13 [95% CI: 0.03, 0.67]) was significantly lower in the bevacizumab group. Refractive astigmatism was significantly lower in the study group (-1.0 ± 1.04 diopters vs 1.82 ± 1.41 diopters; $P = .03$). In multivariate analysis, myopic refractive error and astigmatism were significantly associated with laser therapy vs bevacizumab therapy ($P = .04$ and $P = .02$, respectively).
- **CONCLUSIONS:** In a 1-year follow-up, a single intravitreal bevacizumab injection as compared to conventional retinal laser coagulation was helpful for therapy of ROP and led to less myopization and less astigmatism. (Am J Ophthalmol 2013;155:1119–1124. © 2013 by Elsevier Inc. All rights reserved.)

RETINOPATHY OF PREMATUREITY (ROP) IS A RETINAL ischemic disease in prematurely born infants, and it is characterized by retinal and retinovitreal neovascularization, which eventually leads to tractional retinal detachment. Since vascular endothelial growth factor (VEGF) plays an important role in the pathogenesis of ROP,^{1,2} recent studies have shown the feasibility of the intravitreal use of VEGF inhibitors for the therapy of ROP.^{2–10} In a recent randomized controlled trial, Mintz-Hittner and associates demonstrated that intravitreal bevacizumab monotherapy as compared with conventional laser therapy showed in infants with stage 3+ ROP a significant benefit for zone I disease but not zone II disease.¹⁰ Interestingly, the peripheral retinal vessels continued to develop after treatment with intravitreal bevacizumab, whereas conventional laser therapy led to a permanent destruction of the peripheral retina. It has remained unclear whether the intravitreal bevacizumab therapy as compared to the peripheral retinal laser coagulation leads to the same amount of axial myopization.¹¹ We therefore conducted this study to assess the refractive error of young children who had undergone intravitreal bevacizumab therapy and compared the refractive error of children who had previously undergone laser therapy.

METHODS

THE RETROSPECTIVE NONRANDOMIZED INTERVENTIONAL comparative study included all children who were treated with an intravitreal injection of bevacizumab (Avastin; Genentech Inc, San Francisco, California, USA) for ROP threshold disease in posterior zone II or zone I or for prethreshold ROP in zone I. The study was a retrospective analysis of clinical data obtained during routine care of the children. The Ethics Committee II of the Medical Faculty Mannheim of the Ruprecht-Karls-University Heidelberg approved the study (# 2012-613R-MA). The diagnosis of ROP was based on the revised guidelines of the International Committee for the Classification of Retinopathy of Prematurity.¹² The criterion for therapy of ROP was the presence of a threshold disease, which was defined as disease stage with a 50% likelihood of progressing to retinal detachment. Threshold disease was considered to be present when stage 3 ROP was present in either zone I or zone II, with at least 5 continuous or 8 total clock hours

Accepted for publication Jan 8, 2013.

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of disease, and the presence of plus disease.¹³ Starting in 2008, we discussed with the parents of all affected children the possibility of an off-label intravitreal injection of bevacizumab as an alternative to conventional standard laser treatment performed according to the international guidelines of the Early Treatment for Retinopathy of Prematurity Cooperative Group.¹³ The children of all parents who preferred the intravitreal bevacizumab therapy received that treatment and were included in our study. Informed consent clearly describing the experimental nature of the intravitreal bevacizumab injection was obtained from the parents of all children in the study.

The intravitreal bevacizumab injection was performed under sterile conditions in the pediatric intensive care unit for prematurely born infants. After topical anesthesia of the cornea and conjunctiva by repeated application of oxybuprocaine hydrochloride eye drops and after inducing a slight systemic sedation of the children, the external eye and the surrounding skin were disinfected with a povidone-iodine 5% ophthalmic solution (Betadine; Alcon Inc, Fort Worth, Texas, USA) and the eyes were draped. A lid speculum was inserted. Using a 30-gauge needle, bevacizumab (Avastin) was intravitreally injected at 1.5 mm posterior to the limbus in the temporal inferior quadrant. Because of the relatively small volume injected, an anterior chamber paracentesis was not performed. A reflux of fluid or vitreous was avoided by passing the 30-gauge needle through the sclera in an oblique direction. After the injection, we applied a steroid-antibiotic eye drop combination 4 times per day and atropine 0.5% eye drops twice a day for 1 week. The surgical procedure was performed by 1 of 3 surgeons (B.C.H., F.C.S., W.J.). The study group was compared with a control group of children who had previously undergone retinal argon laser therapy of ROP in the same center. The indications for therapy were the same as for intravitreal bevacizumab injection. Control group and study group did not differ significantly in birth weight, gestational age, and length of follow-up.

The follow-up examinations were carried out by ophthalmologists experienced in diagnosing the disease. The follow-up scheme included daily visits after the injection or the laser therapy until a regression of the neovascularization was detected and the plus disease disappeared. Afterwards, 2 visits per week followed until the neovascularization had completely regressed. Weekly visits ensued up to a gestational age of 42 weeks. At a follow-up examination at about 12 months after birth, all infants were screened for refractive disorders, development of the anterior segment, and the retinal situation. Refractive errors were determined by cycloplegic retinoscopy and automatic refractometry (Autorefractor Portable Retinomax 3; Nikon Corp, Tokyo, Japan) approximately 30 minutes after instilling 1% cyclopentolate hydrochloride (twice with a delay of 10 minutes). For purposes of this study, moderate myopia was defined as a myopic refractive error of ≥ -5 diopters (D) and high myopia was defined as a myopic refractive error of ≥ -8 D.

The description of the posterior pole examination was as follows: normal, abnormally straightened temporal retinal vessels, macular ectopia, retinal fold, partial or complete retinal detachment.

Statistical analysis was performed using a commercially available statistical software package (SPSS for Windows, version 20.0; IBM-SPSS Inc, Chicago, Illinois, USA). Continuous data were presented as mean \pm standard deviation. Prevalence was presented as mean \pm standard error. The normal distribution of parameters was tested using the Kolmogorov-Smirnov test. χ^2 tests were used to compare proportions. Odds ratios (OR) were presented and their 95% confidence intervals (CI) were described. All *P* values were 2-sided and were considered statistically significant when less than .05.

RESULTS

THE STUDY GROUP CONSISTED OF 23 EYES OF 12 CHILDREN (7 boys, 5 girls) with a mean \pm standard deviation birth weight of 622 ± 153 g (median: 590 g; range: 450-1115 g) and a mean gestational birth age of 25.2 ± 1.6 weeks (median: 24.9 weeks; range: 23-29 weeks). Of the 12 children, 3 showed an acute posterior stage of ROP and fulfilled the criteria for treatment according to the guidelines of the Early Treatment for Retinopathy of Prematurity Cooperative Group.¹³ The remaining 9 children showed an ROP stage 3+ with neovascularization in 5 adjacent sectors of 30 degrees width or 8 nonadherent sectors and fulfilled the same criteria for therapy as did the children of the control group. In the first child of our series with aggressive posterior ROP in both eyes, 1 eye with clear optic media received a primary laser treatment and the other eye with a persistent tunica vasculosa lentis underwent an intravitreal injection of bevacizumab. Since the eye with laser therapy continued to develop retinovitreal neovascularization, it received an intravitreal injection of bevacizumab 4 weeks after laser therapy. That eye was not included either in the bevacizumab group or in the laser group. All other infants received a single injection of bevacizumab without any laser therapy prior to, or after, the bevacizumab application. Nine children (treated by B.C.H. and F.C.S.) received a dosage of 0.375 mg bevacizumab. We arrived at the dosage of 0.375 mg bevacizumab by taking one-fourth of the dosage given to an adult eye (about 1.5 mg) and by considering that the eye of an infant makes up about one-fourth of the volume of an emmetropic adult eye. Three children (treated by W.J.) received a dosage of 0.625 mg bevacizumab. The follow-up examination was performed at 11.1 ± 3.1 months of corrected age (median: 10.5 months; range: 7.0-23.0 months). The reason for the different dosages of bevacizumab was that the injection was performed by different surgeons.

The control group included 26 eyes of 13 children (7 boys, 6 girls) with a median birth weight of 717 ± 197 g (median:

690 g; range: 440-1090 g) and a mean gestational birth age of 25.3 ± 1.8 weeks (median: 25.0 weeks; range: 23-28 weeks). The follow-up examination was performed at 11.7 ± 1.6 months (median: 11.5 months; range: 10-14.0 months) of corrected age. Study group and control group did not differ significantly in birth weight ($P = .07$), gestational age at birth ($P = .77$), or length of follow-up ($P = .43$).

All eyes of the study group showed a regression of plus disease within 2 to 6 days after the intravitreal injection; a decrease in pupillary rigidity; a resolution of any tunica vasculosa lentis, if present prior to the injection; and a complete regression of the retinal neovascularization within 2 to 3 weeks. In none of the children was a second intravitreal injection of bevacizumab necessary. None of the eyes of the study group showed signs of an injury to the lens or retina, retinal detachment or vitreous hemorrhage, or intraocular inflammation during the follow-up period. One eye of the laser group developed a partial retinal detachment (stage 4b). The infant who received a primary laser treatment in the right eye and an intravitreal bevacizumab injection 4 weeks later developed a retinal fold and macular ectopia. The left eye, which had received intravitreal bevacizumab only, showed a regression of the tunica vasculosa lentis and of all retinal neovascularizations without any retinal fold or any other morphologic abnormality. At 29 months of corrected age, the refractive error was -10.25 D in the right eye and -8.00 D in the left eye.

At the end of the follow-up period, mean refractive error was significantly less myopic in the study group than in the control group (-1.04 ± 4.24 D [median: 0 D; range: -12.5 to $+4.63$ D] vs -4.41 ± 5.50 D [median: -5.50 D; range: -14.0 to $+4.38$ D]; $P = .02$) (Figure 1). In multivariate analysis with refractive error as dependent parameter and study group, birth weight, sex, and gestational birth age as independent parameters showed that myopic refractive error was significantly associated with laser therapy vs bevacizumab therapy ($P = .04$; regression coefficient: 3.11 [95% confidence interval: 0.11, 6.11]), while birth weight ($P = .55$), sex ($P = .22$), and gestational age at birth ($P = .80$) were not significantly associated with refractive error. In a binary regression analysis with laser therapy vs bevacizumab therapy as dependent variable and refractive error, birth weight, sex, and gestational birth age as independent parameters revealed that laser therapy was significantly associated with myopic refractive error ($P = .04$; OR: 1.15 [95% CI: 1.01, 1.31]), while birth weight ($P = .08$), sex ($P = .29$), and gestational age at birth ($P = .33$) were not significantly associated with the type of therapy. The prevalence of moderate myopia ($17\% \pm 8\%$ [95% CI: 1,34] vs $54\% \pm 10\%$ [95% CI: 33,74]) and of high myopia ($9\% \pm 6\%$ [95% CI: 0,21] vs $42\% \pm 10\%$ [95% CI: 22,63]) was significantly ($P = .02$; OR: 0.18 [95% CI: 0.05, 0.68] and $P = .01$; OR: 0.13 [95% CI: 0.03, 0.67], respectively) lower in the bevacizumab group than in the laser group.

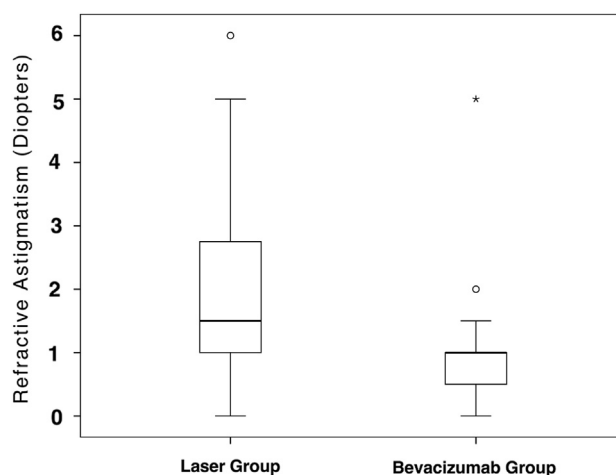


FIGURE 1. Box plot showing the distribution of refractive error in the prematurely born children with retinopathy of prematurity treated either by peripheral retinal laser coagulation or by intravitreal low-dosage bevacizumab injection.

Refractive astigmatism was significantly lower in the study group than in the control group (-1.0 ± 1.04 D [median: 1.0 D; range: 0.0 to 5.0 D] vs 1.82 ± 1.41 D [median: 1.50 D; range: 0.0 to 6.00 D]; $P = .03$) (Figure 2). In multivariate analysis with refractive astigmatism as dependent parameter and study group, birth weight, sex, and gestational birth age as independent parameters revealed that astigmatism was significantly associated with laser therapy vs bevacizumab therapy ($P = .02$; regression coefficient: -0.88 [95% CI: -1.67 , -0.12]), while birth weight ($P = .42$), sex ($P = .99$), and gestational age at birth ($P = .09$) were not significantly associated with refractive error. In a binary regression analysis with laser therapy vs bevacizumab therapy as dependent variable and refractive error, birth weight, sex, and gestational birth age as independent parameters revealed that laser therapy was significantly associated with myopic refractive error ($P = .03$; OR: 0.49 [95% CI: 0.25, 0.95]) and birth weight ($P = .04$; OR: 0.99 [95% CI: 0.99, 1.00]), while sex ($P = .62$) and gestational age at birth ($P = .16$) were not significantly associated with the type of therapy.

DISCUSSION

THE RESULTS REVEALED THAT ALL CHILDREN WHO received a single intravitreal bevacizumab injection showed a favorable anatomic outcome, as indicated by the complete regression of any retinal neovascularization; absorption of vitreous hemorrhage, if present prior to the injection; and regression of a tunica vasculosa lentis. Additional retinal laser coagulation or a repeated intravitreal injection was not necessary in any eye. The effect of the

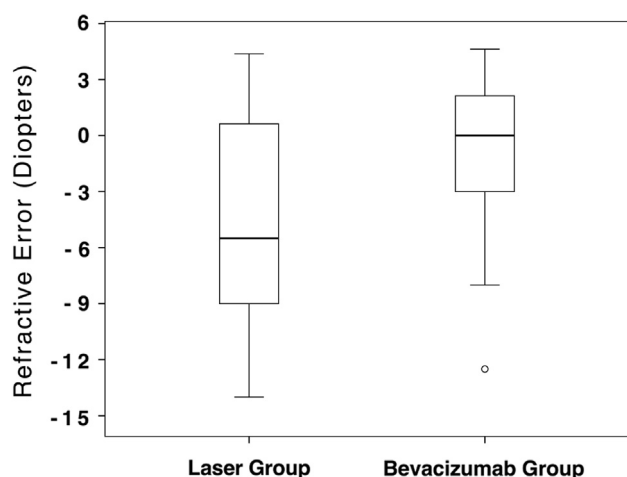


FIGURE 2. Box plot showing the distribution of refractive astigmatism in the prematurely born children with retinopathy of prematurity treated either by peripheral retinal laser coagulation or by intravitreal low-dosage bevacizumab injection.

intravitreal bevacizumab therapy could be observed within 3 days to 3 weeks after the injection. In addition to these morphologic findings, refractometry performed at about 1 year after birth showed a significantly lower prevalence of moderate myopia and high myopia in the bevacizumab group than in a laser group.

The finding of a favorable morphologic outcome after intravitreal bevacizumab therapy for ROP agrees with the previous investigations on the same topic.²⁻¹⁰ The finding of less myopization after medical therapy of ROP as compared to laser therapy confirms a recent pilot study by the same authors on a smaller number of children, with no other investigations publicly available so far. Although the cause for myopization in children treated for ROP has remained unclear so far, the results of our study are in line with previous investigations in which myopization was more pronounced in children randomized for the more invasive cryotherapy than for the less invasive laser therapy.¹⁴ This finding, however, was not obtained in all studies.¹⁵ The process of emmetropization in an infant's eye has still not been entirely understood, nor has been the effect of ROP itself and the impact of cryotherapy and diode laser photocoagulation on the myopization process been elucidated. Lue and associates postulated that the retina in eyes after ROP is rendered dysfunctional, which may affect the eye growth signals, or that ROP might halt or delay the normal migration of photoreceptors from the fovea with an effect on acuity sufficient to alter the visually driven feedback mechanism in emmetropization.¹⁶ Davitt and associates and the Cryotherapy for Retinopathy of Prematurity Cooperative Group reported on an association between increasing myopia and advancing stage of ROP.^{17,18}

A new finding of our study was that the relatively small dosage of 0.375 mg (given in 9 of the 12 children in the study group) appeared to have had an effect similar to the dosage of 0.625 mg applied in the Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) study.¹⁰ If the risk of potential systemic side effects depends on the dosage of the intravitreally injected drug, the finding of our study using approximately only half of the dosage given in the BEAT-ROP study may warrant future dosage-finding investigations. The main concern about bevacizumab for treatment of retinopathy of prematurity remains the uncertainty of systemic and ocular side effects on the physiologic vascularization processes in the eye and in the body in general. In the relatively short follow-up of 1 year in our study, we did not detect any systemic side effects such as arterial hypertension, gastrointestinal hemorrhages, or thrombotic events. This finding of the current study agrees with the BEAT-ROP study, in which a further development of the peripheral retinal vascularization in the infants after the intravitreal injection of bevacizumab was observed.¹⁰ The follow-up in our study was too short to detect growth retardation or other long-term systemic side effects.

A major advantage of the intravitreal bevacizumab application as compared with conventional retinal laser treatment is the less invasive character of the procedure. General anesthesia is not needed, which may be of marked benefit for the infants who otherwise run the risk of a prolonged postoperative period of intubation. In addition, laser therapy leads to a coagulation and destruction of the peripheral retina and parts of the choroid, which may interfere with a normal growth of the globe and may potentially lead to higher rates of myopia. An additional advantage of intravitreal bevacizumab vs retinal laser coagulation is that bevacizumab blocks VEGF, which is already produced and is present in the vitreous body, while a retinal laser coagulation prevents further production of VEGF. The therapeutic effect may thus be earlier with the intravitreal bevacizumab therapy than with the retinal laser coagulation. One may also consider that the retinal coagulation by the laser treatment initially leads to a pronounced retinal inflammation associated with the release of inflammatory cytokines, which will support the neovascularization process.

Potential limitations of our study should be mentioned. First, it was a retrospective study with no randomized control group. The level of scientific evidence is therefore markedly lower than the scientific level of the previous prospective randomized trial by Mintz-Hittner and associates comparing the early outcome after intravitreal bevacizumab with laser therapy in ROP.¹⁰ Despite its retrospective character, however, the present study included all infants who had undergone intravitreal bevacizumab therapy in our center. In addition, one may consider that no other study has yet reported on the refractive error outcome at 1 year after the intervention. Second, although

the follow-up was approximately 1 year, it was still relatively short, so the study does not allow any conclusions about the long-term effects and side effects of the therapy. This may hold true in particular for potential systemic side effects. Third, no statement can be made about the functional outcome after the therapy, since the infants were still too young for any functional test. However, regarding the normal appearance of the retina and the whole eye, it could be assumed that there has not been a marked reduction in function. Fourth, the number of children included was relatively small, which does not allow any statements on the safety of the therapy. Fifth, 3 of 12 children of the bevacizumab study showed an acute posterior stage of ROP, so that they underwent therapy at a high-risk prethreshold stage, in contrast to the children of the control group, who were treated at the classic old-definition threshold ROP. The majority of the bevacizumab study group, however (ie, 9 of 12 children), showed an ROP stage 3+ with neovascularization in 5 adjacent sectors or 8

nonadherent sectors and were thus at the same stage of the disease as the children in the laser control group. It may be considered that although study group and control group were not completely identical at baseline, both groups were comparable up to a certain limit. Strengths of our study were that it is the first follow-up study addressing the refractive error outcome after a follow-up of about 1 year; and that in contrast to all other previous studies on intravitreal bevacizumab as therapy for ROP, the low dosage of 0.375 mg was used.

In conclusion, in a 1-year follow-up, a single intravitreal low-dosage bevacizumab injection as compared to conventional retinal laser coagulation was helpful for therapy of ROP and led to less myopization and less astigmatism. Future randomized trials may address the same topic to strengthen the conclusions of this study, including the finding that the low dosage of 0.375 mg bevacizumab may be sufficient for a complete regression of the intraocular neovascularizations in ROP.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and the following were reported: Jost B. Jonas: board member for Allergan, Merck & Co, and Allimera; patent holder with CellMed AG, Alzenau, Germany. The authors indicate no funding support. Contributions of authors: design and conduct of the study (B.C.H., S.v.B., F.C.S., W.J., B.J., J.B.J.); collection, management, analysis, and interpretation of the data (B.C.H., S.v.B., F.C.S., W.J., B.J., J.B.J.); and preparation, review, or approval of the manuscript (B.C.H., S.v.B., F.C.S., W.J., B.J., J.B.J.).

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Biosketch

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