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Ocular complications following treatment in the Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study

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Abstract

Purpose—To determine the prevalence of treatment-related ocular complications and disease progression following treatment for retinopathy of prematurity (ROP).

Methods—This was a retrospective cohort study of eyes treated for ROP at 30 North American neonatal intensive care units in the Postnatal Growth and ROP (G-ROP) Study. Data from the time of treatment through 15 months were abstracted from medical records by certified data collectors. Treatment-related complication (cataract, hyphema, glaucoma, corneal abrasion/opacity), and disease-progression (retinal fold, dragging, or stage 4 or 5 detachment) were calculated by treatment modality. Vitreous hemorrhage was classified separately, because it can relate to treatment or disease progression.

Results—Of 7,483 infants included in the study, 1,004 eyes (512 infants) underwent ROP treatment: 970 eyes received laser as initial therapy; 34 eyes received intravitreal bevacizumab (IVB). Median follow-up after treatment was 18 weeks. Overall, one or more complications occurred in 2.6% (95% CI, 1.8%-3.8%) laser treated eyes and no (0%; 95% CI, 0.0%-10.1%) IVB eyes. Disease-progression occurred in 9.2% (95% CI, 7.6%-11.2%) laser treated eyes, no (0%; 95% CI, 0.0-12.9%) IVB-only eyes. Vitreous hemorrhage occurred in 5.4% (95% CI: 4.1% - 7.0%) laser treated eyes, no IVB-only eyes.

Conclusions—Rates of complications are very low following ROP treatment with either laser or IVB. Of laser-treated eyes, 9% experienced disease progression despite treatment.

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[*]The G-ROP Study Group is provided in eSupplement 1, available at jaapos.org.

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Retinopathy of prematurity (ROP) is a potentially blinding disease of the eye observed in premature infants.[1,2], caused by poor retinal vascular development.[3] Over the past several decades, laser therapy with panretinal photocoagulation have been used to treat severe ROP and decrease the risk of progression to retinal detachment.[4,5] With this treatment, laser spots are applied to avascular retina to purposefully damage the tissue, decreasing the production of vascular endothelial growth factor (VEGF), the primary causative agent for angiogenesis.[6] With the advent of VEGF inhibitors, such as bevacizumab, a new trend in treating ROP is emerging. The Bevacizumab Eliminated the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) randomized controlled trial demonstrated a greater recurrence of posterior ROP treated with laser photocoagulation versus intravitreal injection of bevacizumab (IVB) and suggested greater ocular complications with laser therapy.[7] However, neonatologists and ophthalmologists have voiced concerns over the potential short- and long-term ocular and systemic effects of bevacizumab, which has been documented to be present in serum samples after an intravitreal injection.[8,9]

The Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study is a large retrospective cohort study with a primary aim of developing a postnatal growth prognostic model to predict severe ROP.[10] Retrospective data were collected from infants at 30 neonatal intensive care units, including types of ROP treatment and outcomes after treatment through 15 months of age. As such, the dataset offers a unique opportunity to determine the incidence of posttreatment ocular complications. The current study performed a secondary analysis of data from the G-ROP Study to determine the rates and types of complications following laser retinal photocoagulation or IVB for the treatment of ROP. The rate of disease progression following treatment for ROP was also assessed.

Subjects and Methods

The design of the G-ROP Study has been reported previously.[10] Briefly, the G-ROP Study was a National Institutes of Health, National Eye Institute-supported, multicenter, retrospective cohort study of infants who underwent ROP screening at 30 hospitals in the United States and Canada. Institutional review board approval for the study was obtained and waiver of informed consent was granted at the study headquarters (Children's Hospital of Philadelphia), the study data coordinating center (University of Pennsylvania), and at all study hospitals (eAppendix).

Subjects were infants born between January 1, 2006, and December 31, 2011, with known birth weight, gestational age, postnatal weight measurements, and ROP outcome, which included the presence in either eye of Early Treatment of Retinopathy (ETROP) Study type 1 or type 2 ROP (any stage ROP in zone I, or stage 3 ROP in zone I or zone II, or plus disease) or treatment performed in either eye. For statistical analysis of treated eyes as type 1 or type 2 ROP, an a priori decision was made to include treated zone III disease with plus disease with type 1 ROP and treated zone III disease without plus with type 2 ROP. Infant demographic, medical, and ophthalmological data were extracted retrospectively from inpatient and outpatient medical records by certified data collectors and entered into a web-based database. Fellowship-trained pediatric ophthalmologists or retinal specialists with ROP expertise completed ophthalmological examinations. Detailed examination data were

collected for every examination through vascular maturity or disease regression, as well as the type and date of all treatments, including laser retinal photocoagulation, cryotherapy, retinal detachment surgery (eg, scleral buckle or vitrectomy), and intravitreal injection of an anti-VEGF agent, with name and dose of agent used. For infants who had received ROP treatment, additional data were collected on complications, including corneal abrasion, ulcer, or opacity; hyphema; cataract; glaucoma; and infection. In addition, disease progression defined as retinal fold, retinal dragging/macular ectopia, stage 4 ROP (4a, 4b, or unspecified), and stage 5 ROP were recorded. If an eye developed stage 4 and continued to progress to stage 5, it was categorized only as a stage 5 eye. Posttreatment complications and disease progression data were collected up to 15 months of chronological age or June 30, 2012, whichever occurred sooner. This date was used because of the date of institutional review board protocol submission. Data quality in the study was ensured through database validation rules, data audits, and discrepancy check algorithms, with investigation and resolution of all flagged values.

Statistical Analysis

Eyes were classified as having received laser retinal photocoagulation only (laser), intravitreal bevacizumab injection only (IVB), or both laser and IVB. The primary outcome was the proportion of treated eyes that had one or more posttreatment complications. All treated eyes (laser, IVB, or both) were considered for this primary outcome, but the rates were stratified by the type of treatment received (laser or IVB). Eyes that had both laser and IVB were categorized as either laser or IVB, according to the first treatment modality used (laser or IVB), and only posttreatment complications that occurred prior to administration of the second treatment modality were considered. For the secondary outcome measure of disease progression, data were analyzed only among infants treated with a single treatment (laser or IVB). Vitreous hemorrhage was considered separately, because it was not easy to discern on review of the medical records whether the hemorrhage occurred primarily as a result of treatment or due to disease progression. The 95% confidence intervals for the complication rates were calculated using the Wilson method.[11] All analyses were made using SAS for Windows v9.4 (SAS Inc, Cary, NC).

Results

A total of 7,483 infants were included in the G-ROP Study; of these, 512 (1004 eyes) were treated for ROP with laser or intravitreal injection of an anti-VEGF agent. Of the 512 cases, 963 eyes of 492 infants were treated only with laser, 26 eyes of 14 infants were treated only with IVB, and 15 eyes of 9 infants were treated with both laser and IVB, of which 7 eyes were first treated with laser and 8 eyes were first treated with IVB. The median (interquartile range) length of follow-up was 18 weeks (range, 5-39 weeks). Baseline demographics by treatment group based on the first treatment appear in Table 1. Mean birthweights were less for infants in the IVB group compared to the laser group (609 g vs 719 g), but gestational ages were similar (Table 1). The ROP characteristics of eyes at the time of first treatment are shown in Table 2. Laser-treated eyes had a higher rate of type 1 ROP (including zone III ROP with plus) than anti-VEGF treated eyes (82.2% vs 73.5%). Of note, approximately 15%

of eyes did not meet type 1 criteria for treatment. The majority of eyes treated without type 1 ROP had pre-plus disease rather than plus disease.

Overall, 25 (2.5%; 95% CI, 1.8%-3.8%) of 970 laser treated eyes had one or more complications (Table 3), while none of the 34 IVB treated eyes had complications (0.0%; 95% CI, 0.0%-10.1%). Hyphema was the most common complication noted, followed by corneal opacity. For calculating rates of disease progression, infants treated with laser only or IVB only were considered. Baseline demographic data by treatment group are outlined in eTable 1. Again, infants treated with IVB only trended toward smaller birth weight (606 g vs 720 g) but less type 1 ROP (eTable 2) compared to laser-only treated infants. Disease progression occurred in 89 of 963 laser-only eyes (9.2%; 95% CI, 7.6%-11.2%) and no IVB-only eyes (0%; 95% CI, 0.0%-12.9%). Specific ROP outcomes are detailed in Table 4. Vitreous hemorrhage occurred in 52 (5.4%; 95% CI, 4.1%-7.0%) laser-only eyes and 0 (0.0%; 95% CI, 0.0%-10.2%) IVB-only eyes.

A post hoc analysis was performed among the 15 eyes that received both laser and IVB. Of 7 eyes that were treated with laser first, 4 eyes subsequently developed stage 4 or 5 ROP despite IVB, and 3 eyes developed vitreous hemorrhage after IVB. One of 8 eyes treated with IVB first had vitreous hemorrhage.

Discussion

The current study found that the rate of complications directly attributable to treatment following laser for ROP was very low (<3%). Among 963 laser-treated eyes in our study, we documented 3 cataracts, 6 cases of corneal opacity, and 15 cases of hyphema. These results are similar to prior studies. The BEAT-ROP study reported 3 cases of cataract and 1 case of corneal opacity after laser treatment, or 2.7% among 146 eyes studied.[7] In the ETROP study, the rate of cataract by 6 months corrected age among 366 eyes that received laser was 1.9%.[12] Of note, an additional 2 eyes in the ETROP study developed cataract following regressed severe ROP that had not been treated.[12] High laser powers may result in cataract or corneal damage during laser treatment, and if iris or anterior segment neovascularization is present and the pupil diameter is small, iris vessel damage by the laser could result in hyphema.

Based on only 41 infants treated with IVB, we found minimal ocular complications of ROP treatment with IVB (1 case of vitreous hemorrhage in an infant treated with IVB first and then laser). The G-ROP Study was a large retrospective cohort study covering the period between 2006 and 2012. The use of IVB for ROP was not widespread during this time period, as demonstrated by the small number of eyes treated with IVB at the study hospitals. Therefore, the study was not powered adequately to detect differences in complication or disease progression rates between eyes that were treated with laser versus IVB for ROP, nor to precisely estimate the rate of complications following IVB for ROP.

There was inadequate statistical power to know whether there is a difference in complication rates for laser and IVB. Regardless, the complication rate following laser was low; thus, any potential difference in ocular complication rates between laser-treated and injected eyes may be of limited clinical significance. In addition, any potential benefit related to lower ocular

complications must be weighed against the risk of systemic adverse effects. It is well established that anti-VEGF agents escape the eye after treatment and enter the bloodstream.[13] Infants treated with IVB have systemic VEGF suppression for several weeks after treatment.[14] It is possible that systemic suppression of VEGF could hinder vascularization of developing brain, lung, kidney, or other tissues that could lead to developmental issues associated with this treatment. Finally, intravitreal injection is associated with a very small risk of endophthalmitis, which is not a risk of laser treatment for ROP.

We found that 9.2% of eyes treated with laser progressed despite treatment for ROP. No eyes receiving IVB progressed, but again this prevalence rate estimate was imprecise with a wide confidence interval, and there was insufficient statistical power to make a comparison to laser treatment. The BEAT-ROP Study[7] was the first to suggest a significant difference between laser and IVB with regards to ROP disease progression after treatment. In the BEAT-ROP study, retreatment rates were 22% after laser and 4% after IVB in infants with zone I or posterior zone II disease. However, multiple studies have demonstrated a much lower recurrence rate after laser than reported in the BEAT-ROP Study.[15–18] From our large number of eyes treated with laser, the observed disease progression rate of 9.2% for laser-only treated eyes lends additional evidence that disease progression after laser treatment in BEAT-ROP may not be indicative of what is commonly seen in practice. In addition, the follow-up length in the BEAT-ROP study extended only to 54 weeks postmenstrual age,[19] and, late, treatment-requiring recurrences following IVB have been reported at 35 weeks after treatment (about 70 weeks' postmenstrual age),[20] and tractional retinal detachment following IVB has been reported at 2.5 years of age.[21] Therefore, the retreatment rate reported for IVB in BEAT-ROP may be an underestimate. Finally, an absence of disease progression alone may not be adequate predictor of final visual function. A randomized controlled trial of 12 infants, in which each infant had one eye treated with IVB and the second eye treated with laser, found that all eyes treated with IVB demonstrated peripheral and macular vascular abnormalities on fluorescein angiography 9 months after treatment, whereas the majority of laser-treated eyes did not demonstrate these abnormalities.[22]

The incidence of vitreous hemorrhage was not reported in BEAT-ROP.[7] Hwang and colleagues reported similar rates of vitreous hemorrhage in eyes treated with IVB versus laser.[20] It is unclear why nearly all episodes of vitreous hemorrhage occurred in laser-treated eyes in our study (52 of 963 eyes treated with laser versus 1 eye treated with bevacizumab first in the laser+IVB group). One might hypothesize that the presence of VEGF in combination with the pro-inflammatory nature of laser is more likely to cause bleeding. However, disease progression was also present in some laser-treated eyes, which could also account for this complication. The cause of vitreous hemorrhage in the IVB-treated eye was unclear based upon retrospective review of the medical record.

Strengths of our study include the very large number of laser-treated eyes and a diverse, multicenter cohort representative of infants being treated for ROP in North America. Our study also has several important limitations. First, this study was not designed to compare laser versus IVB, and many fewer eyes were treated with IVB, limiting the statistical power with which to compare the modalities. Second, clinical findings were recorded in a nonstandardized fashion; however, the ophthalmologists performing routine posttreatment

clinical follow-up examinations could be expected to reliably identify and document the presence of complications. Third, infants were not randomized to the treatment type, so selection bias by treating physicians could have been introduced. It is not clear how such bias might influence the study results. Additionally, some infants were treated with a sequential combination of therapies. Several of the infants treated with IVB first were subsequently treated with laser in the absence of disease progression, presumably to avoid the risk of late reactivation of disease.[3] Therefore, it is possible that IVB-treated eyes may have demonstrated disease progression had laser not been done, and the rate of complications for IVB-only eyes would have been higher. Fourth, we did not evaluate late reactivation rates after IVB treatment as follow-up times were not mandated in this retrospective study. Refractive or developmental outcomes after treatment for either group also were not evaluated, nor were complications resulting from sedation administered for ROP treatment, which might be more common with laser, as laser takes considerably longer to complete than intravitreal injection. Finally, 15% of infants were treated without documented evidence of type 1 ROP. Treatment of infants without type 1 ROP in clinical practice has been reported to occur in about 10% of cases for reasons such as contralateral disease and advanced postmenstral age.[23] In our retrospective data, we felt it was important to include all infants treated for ROP. Treatment was performed at the discretion of the ophthalmologist, and the treating physician may have believed that an infant would benefit from earlier treatment in these cases.

In a diverse, multicenter retrospective cohort study of infants at 30 North American hospitals, post-treatment ocular complications appeared to be very uncommon with both laser and IVB. There was inadequate statistical power to compare rates of complications or disease progression between laser and IVB. Generally, further study is needed to more precisely describe the ocular complication and retreatment rates following IVB for ROP as well as to assess the potential nonocular adverse developmental effects and the risk of endophthalmitis following IVB, particularly as the rate of laser-associated complications appears to be very low. When facing a treatment decision, ROP zone and severity and the systemic health of the infant should be evaluated to determine the best treatment for each individual case until prospective comparative data of the longer-term effects of IVB and laser are available.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographics by treatment group of the first treatment

Demographic characteristic	Laser (n = 494 infants)	Anti-VEGF (n = 18 infants)	Total (n = 512 infants)[a]
Birth weight, g			
Mean ± SD	719 ± 206	609 ± 127	715 ± 205
Median (1st quartile, 3rd quartile)	671 (574,820)	600 (570,660)	670 (574,816)
Gestational age, weeks			
Mean ± SD	25 ± 2	25 ± 1	25 ± 2
Median (1st quartile, 3rd quartile)	25 (24,26)	25 (23,25)	25 (24,26)
Sex			
Female	219 (44.3)	7 (38.9)	226 (44.1)
Male	275 (55.7)	11 (61.1)	286 (55.9)
Ethnicity (%)			
Hispanic or Latino	46 (9.3)	0 (0.0)	46 (9.0)
Not Hispanic or Latino	263 (53.2)	12 (66.7)	275 (53.7)
Unknown	185 (37.4)	6 (33.3)	191 (37.3)
Maternal race (%)			
White	257 (52.0)	8 (44.4)	265 (51.8)
Asian/Asian American	13 (2.6)	3 (16.7)	16 (3.1)
Black/African American	113 (22.9)	1 (5.6)	114 (22.3)
American Indian/Alaskan Native	4 (0.8)	0 (0.0)	4 (0.8)
Native Hawaiian/other Pacific Islander	3 (0.6)	0 (0.0)	3 (0.6)
Other	45 (9.1)	2 (11.1)	47 (9.2)
Unknown	59 (11.9)	4 (22.2)	63 (12.3)

[a]Three infants had two eyes in two different treatment groups; thus, the total number of infants is not equal to the sum of number of infants in each treatment group.

Table 2

ROP features at time of first treatment

ROP Features	Laser (n = 970 eyes)	Anti-VEGF (n = 34 eyes)	Total (n = 1004 eyes)
Type 1 ROP and zone III ROP with plus, no. (%)	798 (82.3)	25 (73.5)	823 (82.0)
Stage 3, zone I, plus	77 (7.9)	4 (11.8)	81 (8.1)
Stage 2, zone I, plus	10 (1.0)	1 (3.0)	11 (1.1)
Stage 3, zone I, pre-plus	24 (2.5)	1 (2.9)	25 (2.5)
Stage 3, zone I, no plus	15 (1.6)	0 (0.0)	15 (1.5)
Stage 1, zone I, plus	6 (0.6)	1 (2.9)	7 (0.7)
Stage 3, zone II, plus	529 (54.5)	16 (47.1)	545 (54.3)
Stage 2, zone II, plus	74 (7.7)	2 (5.9)	76 (7.6)
Stage 3, zone III, plus	5 (0.5)	0 (0.0)	5 (0.5)
Stage 2, zone III, plus	4 (0.4)	0 (0.0)	4 (0.4)
Type 1 ROP – NS, no. (%)	54 (5.6)	0 (0.0)	54 (5.4)
Type 2 ROP and zone III ROP without plus, no. (%)	144 (14.9)	8 (23.5)	152 (15.1)
Stage 2, zone I, Pre-plus	3 (0.3)	0 (0.0)	3 (0.3)
Stage 2, zone I, no plus	1 (0.1)	0 (0.0)	1 (0.1)
Stage 1, zone I, no plus	1 (0.1)	0 (0.0)	1 (0.1)
Stage 3, zone II, Pre-plus	93 (9.6)	7 (20.6)	100 (10.0)
Stage 3, zone II, no plus	32 (3.3)	1 (2.9)	33 (3.3)
Stage 3, zone III, Pre-plus	2 (0.2)	0 (0.0)	2 (0.2)
Stage 3, zone III, no plus	2 (0.2)	0 (0.0)	2 (0.2)
Type 2 ROP NS, no. (%)	10 (1.0)	0 (0.0)	10 (1.0)
Other ROP, no. (%)	28 (2.9)	1 (2.9)	29 (2.9)
Stage 2, zone II, pre-plus	9 (0.9)	0 (0.0)	9 (0.9)
Stage 2, zone II, no plus	9 (0.9)	0 (0.0)	9 (0.9)
Stage 1, zone III, plus	2 (0.2)	0 (0.0)	2 (0.2)
Other ROP, no. (%)	8 (0.8)	1 (2.9)	9 (0.9)

NS, not specified.

Table 3

Treatment-related complications after first ROP treatment by treatment group

Treatment-related complications	Laser (n = 970 eyes)	Anti-VEGF (n = 34 eyes)	Total (N = 1004 eyes)
Cataract	3 (0.3%)	0 (0.0%)	3 (0.3%)
Hyphema	15 (1.6%)	0 (0.0%)	15 (1.5%)
Glaucoma	1 (0.1%)	0 (0.0%)	1 (0.1%)
Corneal abrasion or ulcer	1 (0.1%)	0 (0.0%)	1 (0.1%)
Corneal opacity	6 (0.6%)	0 (0.0%)	6 (0.6%)
Any above treatment-related complication(s)	25 (2.6%)	0 (0.0%)	25 (2.5%)
95% confidence interval	1.8%–3.8%	0.0%–10.1%	1.7%3.7%

Table 4

Retinopathy of prematurity (ROP) outcomes after treatment for laser only eyes and anti-VEGF only eyes

ROP outcomes after treatment	Laser only (n = 963)	Anti-VEGF only (n = 26)	Total (n = 989)
Retinal fold	11 (1.1%)	0 (0.0%)	11 (1.1%)
Retinal dragging	37 (3.8%)	0 (0.0%)	37 (3.7%)
Stage 4 ROP	33 (3.4%)	0 (0.0%)	33 (3.3%)
Stage 5 ROP	25 (2.6%)	0 (0.0%)	25 (2.5%)
Any above ROP outcome	89 (9.2%)	0 (0.0%)	89 (9.0%)
95% confidence interval	7.6%–11.2%	0.0%–12.9%	7.4%–10.9%