Refractive outcomes comparing primary laser to primary bevacizumab with delayed laser for type 1 ROP

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PURPOSE To compare the refractive outcomes of intravitreal bevacizumab (IVB) and delayed peripheral retinal photocoagulation (PRP) with primary PRP in infants treated for posterior type 1 ROP.

METHODS The medical records of 87 infants at a tertiary referral center treated for posterior type 1 ROP between 2006 and 2016 were reviewed retrospectively. Consecutive infants received primary PRP before and primary IVB after a change in treatment practice implemented in early 2011. In most cases primary IVB was supplemented with prophylactic laser treatment after 60 weeks' PMA (IVB-PRP). The main outcome was spherical equivalent (SE) in diopters, determined by cycloplegic refraction between 2 and 4 years. Infants treated with IVB-PRP were also compared to the those who received only IVB as monotherapy.

RESULTS The final analysis included 34 eyes of 19 infants in the primary PRP group and 40 eyes of 21 infants in the IVB-PRP group. Mean SE was -7.4 ± 5.2 D in the primary PRP group and -0.16 ± 2.2 D in the IVB-PRP group ($P < 0.001$). This relationship persisted after stratification by zone of ROP and the presence of aggressive posterior ROP. There was no statistically significant difference in mean SE between the IVB-PRP group and the 8 eyes of 4 infants who received IVB as monotherapy. Of 46 infants who received primary IVB, 37 completed an examination under anesthesia after 60 weeks' PMA. In these patients, 70% of eyes showed peripheral vascular leakage on fluorescein angiography.

CONCLUSIONS In our study cohort, infants treated with IVB-PRP were significantly less myopic than those treated with primary PRP. Delayed laser after 60 weeks' PMA, in hopes of reducing the risk of late reactivation with retinal detachment, did not negate the refractive benefits of primary IVB. (J AAPOS 2019;23:88.e1-6)

Since the publication of BEAT-ROP (Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity) in 2011, use of intravitreal bevacizumab (IVB) has become increasingly common for the treatment of posterior type 1.[1] Compared to primary peripheral retinal photocoagulation (PRP), IVB provides significantly lower rates of recurrence and macular dragging as well as superior refractive outcomes.[1,2] By avoiding permanent destruction of the peripheral retina, IVB may also spare peripheral vision.[3] Additionally, IVB avoids the need for general anesthesia in the neonatal period, which is often necessary with peripheral retinal photocoagulation.

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Disadvantages of IVB include the risk of late reactivation of ROP, with the need for lengthy monitoring after initial IVB treatment.[4-7] Traditionally infants with regressed ROP have been considered at low risk for recurrence after 50-60 weeks' postmenstrual age (PMA).[8] After IVB treatment, however, complete retinal vascularization by 54 weeks is rare, with a high rate of leakage on fluorescein angiography.[9-11] Given case reports of retinal detachment (RD) secondary to ROP reactivation after IVB monotherapy in toddlers,[6,7] the appropriate endpoint for ROP monitoring after IVB monotherapy remains controversial.[4,5,12] Fluorescein angiography followed by prophylactic laser treatment to persistent avascular retina after 60 weeks' PMA has been recommended to prevent late RD.[9]

The purpose of this study was to compare refractive outcomes of infants with posterior type 1 ROP treated with primary IVB followed by delayed, prophylactic peripheral retinal photocoagulation (IVB-PRP) with those of infants treated with primary PRP. We hypothesized that patients in the former group would have significantly less myopia than those in the latter group.

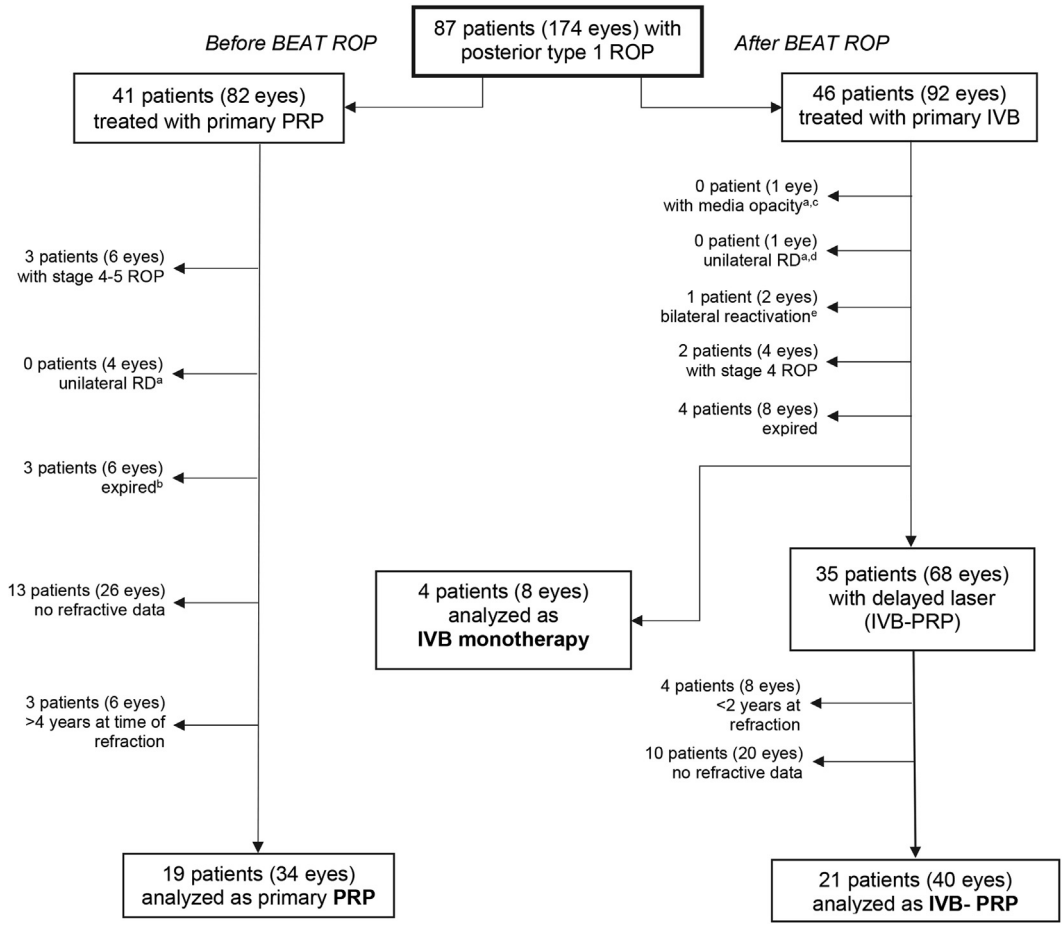

FIG 1. Infants treated for posterior type 1 ROP at the University of Chicago before and after the publication of BEAT-ROP. Infants were treated with laser before and intravitreal bevacizumab (IVB) after the publication of BEAT-ROP. Eyes were excluded if they subsequently progressed to retinal detachment (RD) or required vitrectomy. Eyes were also excluded if the cycloplegic refraction was not completed between 2-4 years of age. Notes: [a]Designation of 0 patients indicates that the fellow eye was included in the study. [b]Four total patients died in the laser group; 1 patient was included who expired after refraction at the age of 2 years. [c]Infant had unilateral endogenous endophthalmitis. [d]Infant had unilateral late retinal detachment with subsequent vitrectomy. [e]Infant had bilateral ROP reactivation, repeat injections, unilateral vitreous hemorrhage, and vitrectomy with early laser to the fellow eye.

Subjects and Methods

This study was approved by the University of Chicago Medical Center Institutional Review Board and conformed to the requirements of the US Health Insurance Portability and Accountability Act of 1996. Based on a clinically motivated treatment shift after the publication of BEAT-ROP in 2011, a retrospective study was designed to evaluate refractive outcomes among consecutive infants treated for ROP at the University of Chicago Medical Center/Comer Children's Hospital before and after switching from primary PRP to primary IVB. For all patients who received primary IVB, examination under anesthesia with fluorescein angiography was recommended after 60 weeks' postmenstrual age (PMA), with prophylactic laser for eyes that showed peripheral nonperfusion or vascular leakage. The paper (prior to July 1, 2012) and electronic (after July 1, 2012) medical records of infants examined over a 10-year period from 2006 to 2016 were reviewed retrospectively to identify those treated for posterior type 1 ROP (zone I and posterior zone II). See Figure 1.

Treated eyes were included only if cycloplegic refractions were documented between 2-4 years of age. Patients who had refractive data outside that age range were analyzed separately. Patients were excluded from analysis if they had RD, lens opacity, or retina surgery. Outcomes were unavailable for some patients, either because refractive data were not available after the transition to electronic medical records, or because patients were unable to complete follow-up at our institution because of insurance changes and other barriers to care commonly encountered among our patients, including lack of transportation, potential loss of productivity for the caregivers, or frequent changes in phone number and contact information.

The primary outcome measure was spherical equivalent (SE) in diopters as determined by cycloplegic refraction at 2-4 years of age. Outcomes were stratified by zone of ROP at primary treatment, as well as the presence or absence of aggressive posterior ROP (APROP) or standard ROP. Infants who received primary PRP were compared to infants who received primary IVB with delayed laser (IVB-PRP). In addition, infants treated with IVB-

PRP were compared to the subset who received only IVB as monotherapy.

Findings on Retcam III–assisted intravenous fluorescein angiography (IVFA) prior to prophylactic laser were also described (Clarity Medical Systems Inc, Pleasanton, CA). The extent of retinal nonperfusion was characterized in terms of mean disk diameters (DD) nasally and temporally. Blair and colleagues[13] have reported that mean nonperfusion from the ora serrata in healthy children was 0.6 DD (range, 0.25–1.0 DD) nasally and 0.9 DD (range, 0.5–1.5 DD) temporally; based on the standard deviation, the authors concluded that 2 DD or more should be considered a sign of peripheral nonperfusion. Toy and colleagues[11] also suggested that ROP treatment should be considered fully successful only if vascularization reached 2 DD of the ora serrata. Accordingly, at least 2 DD of peripheral nonperfusion was considered abnormal in this study.

Data Analysis

Statistical analysis was performed using Stata 15 (StataCorp LP, College Station, TX). Percentages and means with standard deviations were calculated for summary data. Median values with interquartile range (IQR) were also reported. For baseline data, *P* values were calculated using the Fisher exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. To compare spherical equivalent refractive error, a mixed-effects regression model was used to account for the fact that both eyes of the same patient are correlated. The threshold for statistical significance was set at $P \leq 0.05$.

Results

A total of 87 infants were identified for possible inclusion (primary PRP, n = 41; primary IVB, n = 46). Cycloplegic refractions were documented between 2-4 years of age for 44 patients, including 19 (34 eyes) after primary PRP, 21 (40 eyes) after IVB-PRP, and 4 (8 eyes) with IVB monotherapy. Patients who had refractive data outside the 2- to 4-year age range included 3 patients (6 eyes) with primary PRP and 4 patients (8 eyes) with IVB-PRP. Baseline characteristics of the study population are shown in Table 1.

There were no differences in severity of ROP by treatment group; a similar proportion of patients in the primary PRP and IVB-PRP groups had zone 1 ROP or APROP at the time of treatment. Mean age at the time of cycloplegic refraction was not significantly different between the two groups.

The box plot of Figure 2 illustrates the difference in median SE between IVB-PRP eyes and primary PRP eyes. Overall, median SE was +0.25 (IQR, −1 to +1.5) in IVB-PRP eyes versus −7.4 (IQR, −4 to −11) in primary PRP eyes. After stratifying by zone and ROP type at the initial treatment, the difference in refractive error remained significant for eyes with zone I ROP, zone II ROP, APROP, and standard ROP.

Table 2 provides the regression coefficients from the mixed effects linear regression, which accounts for the correlation between eyes of the same infant. After adjusting for birth weight in grams (BW), gestational age in weeks (GA), and age at refraction, infants who received primary PRP were −8.43 D more myopic than infants who received IVB-PRP ($P < 0.001$). This relationship had the strongest effect for infants with zone 1 ROP (adjusted regression coefficient −12.2; $P < 0.001$).

Median SE for infants who received IVB without subsequent laser was −0.50 (IQR, −0.75 to +0.75), which was not significantly different from the refractive error among infants who received IVB-PRP ($P = 0.914$).

Of the infants treated with primary IVB, 37 completed an examination under anesthesia with IVFA, of whom 35 additionally received delayed laser. Angiograms were reviewed for 54 eyes of 28 patients, with the specific DD of

Table 1. Baseline characteristics of infants and eyes in the primary PRP group versus the IVB-PRP group

	Primary PRP (n = 19 infants)	IVB-PRP (n = 21 infants)	*P* value[a]
BW, median (IQR), g	694 (582-820)	652 (625-700)	0.579
GA, median (IQR), weeks	25 (24-28)	24.6 (24-25.3)	0.412
Zone 1 ROP, eyes (%)[b]	12/34 (35)	18/40 (45)	0.479
Zone 2 ROP, eyes (%)[b]	22/34 (65)	22/40 (55)	0.479
APROP, eyes (%)[c]	7/34 (21)	10/40 (25)	0.784
Standard ROP, eyes (%)[c]	27/34 (79)	30/40 (75)	0.784
Age at refraction, median (IQR), years	3 (2.5-3.5)	2.5 (2-3.5)	0.305

APROP, aggressive posterior ROP; *BW*, birth weight; *GA*, gestational age; *IQR*, interquartile range; *IVB-PRP*, intravitreal bevacizumab with delayed peripheral retinal photocoagulation; *ROP*, retinopathy of prematurity.
[a]Fisher exact test for proportions; rank-sum test for difference in means.
[b]Zone 1 and 2 refer to the posterior termination of retinal vasculature at the time of initial treatment.
[c]APROP and standard ROP designate the presence of either aggressive posterior ROP or standard ROP at the time of initial treatment.

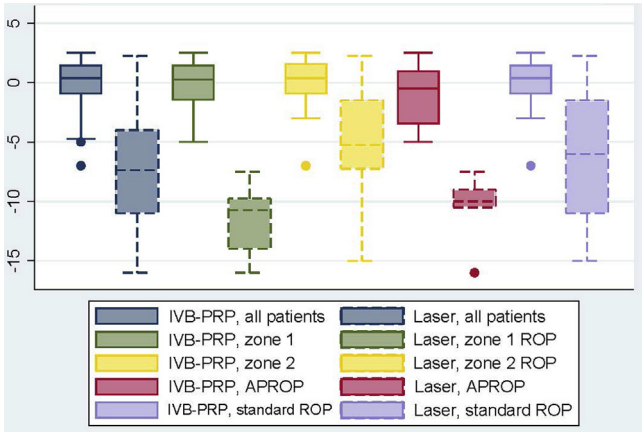

FIG 2. Spherical equivalent by treatment group and severity of ROP. *APROP*, aggressive posterior ROP; *IQR*, interquartile range; *IVB*, intravitreal bevacizumab; *ROP*, retinopathy of prematurity. The box plot shows median (IQR) spherical equivalent refractive error in diopters by treatment group and type of ROP prior to initial treatment.

Table 2. Regression analysis of spherical equivalent refractive error for primary PRP versus IVB-PRP

Primary PRP vs IVB-PRP	Regression coefficient (95% CI)	*P* value[a]	Adjusted coefficient (95% CI)	*P* value[b]
All patients (n = 74)	−7.63 (−5.3 to −10.0)	<0.001	−8.43 (−6.1 to −11.0)	<0.001
Zone 1 (n = 30)[c]	−11.5 (−9.0 to −14.0)	<0.001	−12.2 (−9.6 to −14.9)	<0.001
Zone 2 (n = 44)[c]	−5.45 (−2.7 to −8.3)	<0.001	−6.00 (−2.6 to −9.4)	<0.001
APROP (n = 17)[d]	−9.90 (−6.1 to −13.7)	<0.001	−9.77 (−4.7 to −15.0)	<0.001
Standard ROP (n = 57)[d]	−7.16 (−4.4 to −9.9)	<0.001	−8.04 (−5.3 to −11.1)	<0.001

APROP, aggressive posterior ROP; *CI*, confidence interval; *IVB-PRP*, intravitreal bevacizumab with delayed peripheral retinal photocoagulation; *PPRP*, primary peripheral retinal photocoagulation; *ROP*, retinopathy of prematurity.
[a]Mixed-effects linear regression model controlling for 2 eyes of the same patient.
[b]Mixed-effects linear regression model controlling for 2 eyes of the same patient as well as gestational age, birth weight, and age at refraction.
[c]Zone 1 and 2 refer to the posterior termination of retinal vasculature at the time of initial treatment.
[d]APROP and standard ROP designate the presence of either aggressive posterior ROP or standard ROP at the time of initial treatment.

Table 3. Comparison of baseline characteristics of included and excluded subjects

	Included (n = 40 infants)	Excluded[a] (n = 43 infants)	*P* value[b]
BW, median (IQR), g	679 (593-780)	652 (575-815)	0.695
GA, median (IQR), weeks	25 (24-26)	25 (24-26)	0.534
Zone 1 ROP, eyes (%)[c]	30/74 (41%)	34/92 (37%)	0.748
Zone 2 ROP, eyes (%)[c]	44/74 (59%)	58/92 (63%)	0.748
APROP, eyes (%)[d]	17/74 (23%)	23/92 (25%)	0.856
Standard ROP, eyes (%)[d]	57/74 (77%)	69/92 (75%)	0.856
Laser treatment, eyes (%)	34/74 (46%)	48/92 (52%)	0.637
Stage 4 or 5 ROP, eyes (%)[d]	0/74 (0%)	10/92 (11%)	0.002

APROP, aggressive posterior ROP; *BW*, birth weight; *GA*, gestational age; *IQR*, interquartile range; *ROP*, retinopathy of prematurity.
[a]Includes 46 eyes of 23 patients without refractive data, 10 eyes of 5 patients with bilateral advanced ROP prior to initial treatment, 2 eyes of 1 patient with bilateral ROP reactivation, 5 fellow eyes excluded for retinal detachment, 1 fellow eye excluded for lens opacity, 14 eyes of 7 patients whose refractive data were analyzed separately due to age, and 14 eyes of 7 patients who expired prior to refraction.
[b]Fisher exact test for proportions; rank-sum test for difference in means.
[c]Zone I and II refer to the posterior termination of retinal vasculature at the time of initial treatment.
[d]APROP, standard ROP, and stage 4 or 5 ROP designate the presence of either aggressive posterior ROP or standard ROP at the time of initial treatment.

peripheral nonperfusion noted for 37 eyes of 19 patients. Overall, 38 of 54 eyes (70%) had leakage on angiography, including 14 of 14 eyes with APROP. In addition, 32 of 37 eyes (86%) had at least 2 DD of nonperfusion temporally. Although the small sample size lacked power to demonstrate a significant relationship between SE and DD of avascular retina, IVB eyes with >2 DD of nonperfusion were, on average, −1.1 D more myopic than those with <2 DD ($P = 0.019$).

Results for patients who did not receive refraction within the time frame of 2-4 years were analyzed separately as "younger" and "older" patients. In the primary PRP group, 3 patients (6 eyes) returned to clinic between 5-8 years of age, with a mean SE of –11.95 ± 4.08 (range, −7 to −19). In the IVB-PRP group, 4 patients (8 eyes) were younger than 2 at the study conclusion, with a mean SE of −1.20 ± 2.9 D (range, −8 to +1 D) compared to study group ($P = 0.187$). Excluding one outlier whose SE was −8.00 in both eyes, mean SE in the younger patients was −0.25 ± 1.3 D, with no significant difference compared to the study group ($P = 0.678$). The outlier patient had repeat injections 2 weeks after the primary injection and had >5 DD of nonperfusion at the time of laser treatment at 45 weeks' PMA.

Baseline characteristics of excluded infants are shown in Table 3. Excluded eyes included 46 eyes of 23 patients without refractive data, 10 eyes of 5 patients with bilateral advanced ROP prior to initial treatment, 2 eyes of the same patient with bilateral ROP reactivation, 5 fellow eyes excluded for unilateral RD, 1 fellow eye excluded for lens opacity, 14 eyes of 7 patients whose refractive data were analyzed separately because of age, and 14 eyes of 7 patients who expired prior to refraction. (The remaining 8 eyes of 4 patients were patients in the IVB monotherapy group.) There were no differences in BW, GA, or ROP severity in the excluded versus included patients. A similar proportion of patients lacked follow-up in each treatment group. Because retinal detachment was one of the exclusion criteria, excluded infants were more likely to have stage 4 or 5 ROP.

Of eyes treated before BEAT-ROP, 10 were excluded because of stage 4-5 ROP or RD; of those treated after BEAT-ROP, 8 were excluded, including 4 for stage 4 ROP requiring vitrectomy. One infant had unilateral late RD and subsequent vitrectomy, with follow-up elsewhere, as described previously.[6] Another had endogenous unilateral endophthalmitis; the fellow eye is included.[14] The final patient had bilateral ROP reactivation, repeat injections,

unilateral vitreous hemorrhage, vitrectomy, and early laser application to the fellow eye; refractive data was unavailable for either eye.

Discussion

As with an earlier study comparing refractive outcomes of IVB monotherapy and primary laser in the BEAT-ROP cohort, we found significantly less myopia in the IVB-PRP group than in the primary laser group.[2] This strong association persisted after stratifying by ROP zone and presence of APROP at initial treatment. Given the high rate of leakage and nonperfusion after primary IVB treatment, delayed laser has been recommended to prevent late ROP reactivation and subsequent retinal detachment.[9,11] The results of the present study suggest that delayed laser may prevent late RD without compromising the refractive benefits of primary IVB.

In addition to protecting against late ROP reactivation, primary IVB with delayed laser may also benefit the peripheral vision. Since IVB-PRP allows for more peripheral vascularization of the retina prior to terminal laser therapy, delayed laser may adversely affect peripheral vision less than primary PRP, although a visual field analysis would be necessary to confirm the functionality of the peripheral retina after anti-VEGF therapy. IVB may also decrease the risk of late angle-closure glaucoma, which has been reported with primary PRP.[15]

The nearly 8 D difference in SE between our two study groups is not only highly statistically significant but also of clinical importance. Refractive error is the leading cause of visual impairment among children.[16-24] Bilateral refractive amblyopia may occur in the presence of 5 D or more of myopia, which includes the entire interquartile range of primary PRP patients and none of the IVB-PRP patients. Despite appropriate optical correction, stereoacuity may remain subnormal in patients with high spherical equivalent refractive errors despite improvement in visual acuity.[25] Even without amblyopia, uncorrected distance vision can impair general functioning, diminish school performance, and decrease the economic productivity of adult caregivers.[26]

Because of concerns about late reactivation and RD, all patients treated with primary IVB at our institution have been recommended examination under anesthesia with IVFA. Of the 4 patients in the IVB monotherapy group, one patient's family agreed to EUA, IVFA, and laser, combined with strabismus surgery at age 4. Two others completed the EUA and IVFA previously with minimal leakage and ≤2 DD nonperfusion; parents opted for close monitoring. The final patient is almost 7 years old, and parents prefer to attempt an oral fluorescein with wide-field imaging in the future.

Several theories may explain the refractive benefits of delayed laser compared with primary laser. First, the degree of myopia after primary laser has been correlated with the number of laser spots.[2] Whereas laser is usually applied to zone I and posterior zone II during primary treatment, prophylactic laser after primary IVB is most frequently reserved for anterior zone II or zone III. Older age at the time of prophylactic laser may also contribute to the efficacy of postponed laser treatment. Primary PRP is typically administered between 36-38 weeks PMA,[27,28] whereas delayed laser is recommended after 60 weeks' PMA.[9] Because the myopia that develops after PRP for ROP is refractive and not axial in nature, it is thought to be associated with changes in corneal curvature, lens thickness, and anterior chamber depth.[2] Primary PRP may also interfere with normal anterior segment maturation.[29-31] Perhaps the anterior segment is particularly vulnerable to laser during the first few months of life, and delaying laser an additional 5-6 months protects against excessive myopia.

We also speculate that changes in choroidal circulation may play a role in the progression of myopia after primary PRP. If ablation not only prevents the development of retinal circulation anterior to the equator but also decreases anterior choroidal blood flow, then low partial pressure of oxygen in the anterior vitreous, lens, and anterior segment may occur (Greenwald MJ. IOVS 1986;27[3/suppl]: ARVO abstract 146). Because IVB should have a minimal effect on choroidal circulation while allowing for anterior retinal vascularization—even if it is not associated with microscopically and functionally normal retina—improved delivery of oxygen to more anterior structures may occur.

As a retrospective, nonrandomized chart review, this study has several limitations. The small number of subjects and lack of masking of observers could lead to erroneous data, and 2 years is a long time frame for study inclusion. However, there was no significant difference in age at refraction, and we believe that the adjusted regression model controlled for this variable. Although two previous retrospective studies have not found compelling evidence for the use of IVB monotherapy over primary PRP, IVB was generally reserved for infants with zone I ROP or whose fragile systemic status made general anesthesia undesirable.[3,32] In the present study, the strict before-and-after study design minimized selection bias. Finally, data collection was limited by incomplete medical records. In both treatment groups, however, a similar percentage of patients (13/41 with primary PRP and 10/46 with IVB-PRP) were missing refractive data. Psychosocial factors affecting an inner-city population, such as insurance-related changes requiring transfers of care, lack for transportation, and the opportunity cost of lost productivity to the caregiver, were equally distributed across both treatment groups in our patient population. Given these limitations, more studies are needed to confirm the results of our preliminary analysis. Despite these limitations, our results constitute preliminary evidence that ROP treated primarily with IVB does not cause myopia, even when followed by delayed PRP, and add to existing evidence on the advantages of primary IVB treatment and the potential value of delayed laser.

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