# OUTCOMES AFTER LASER VERSUS COMBINED LASER AND BEVACIZUMAB TREATMENT FOR TYPE 1 RETINOPATHY OF PREMATURITY IN ZONE I

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**Purpose:** To investigate the anatomical and refractive outcomes in patients with Type 1 retinopathy of prematurity in Zone I.

**Methods:** The medical records of 101 eyes of 51 consecutive infants with Type 1 retinopathy of prematurity in Zone I were analyzed. Infants were treated by conventional laser photocoagulation (Group I), combined intravitreal bevacizumab injection and Zone I sparing laser (Group II), or intravitreal bevacizumab with deferred laser treatment (Group III). The proportion of unfavorable anatomical outcomes including retinal fold, disc dragging, retrolental tissue obscuring the view of the posterior pole, retinal detachment, and early refractive errors were compared among the three groups.

**Results:** The mean gestational age at birth and the birth weight of all 51 infants were 24.3 ± 1.1 weeks and 646 ± 143 g, respectively. In Group I, an unfavorable anatomical outcome was observed in 10 of 44 eyes (22.7%). In contrast, in Groups II and III, all eyes showed favorable anatomical outcomes without reactivation or retreatment. The refractive error was less myopic in Group III than in Groups I and II (spherical equivalent of −4.62 ± 4.00 D in Group I, −5.53 ± 2.21 D in Group II, and −1.40 ± 2.19 D in Group III; $P < 0.001$).

**Conclusion:** In Type 1 retinopathy of prematurity in Zone I, intravitreal bevacizumab with concomitant or deferred laser therapy yielded a better anatomical outcome than conventional laser therapy alone. Moreover, intravitreal bevacizumab with deferred laser treatment resulted in less myopic refractive error.

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Retinopathy of prematurity (ROP), a vasoproliferative retinopathy that affects preterm infants who have immature retinal vasculature, remains a leading cause of permanent blindness and visual impairment in children.[1,2] As younger preterm infants are able to survive because of advances in neonatal intensive care, the number of infants at risk for ROP is increasing.[3–5] Extremely preterm infants with low birth weight may develop Zone I ROP.[6–9] Although the overall anatomical and visual outcomes of ROP have improved because of proper screening and laser treatment, the outcome of treatment for Zone I ROP is still unsatisfactory.[10–12] A significant number of eyes with Zone I ROP still show retinal detachment (RD), ranging from 18.2% to 75.0%, after laser treatment.[10,12,13] Additionally, eyes that have undergone laser treatment for Zone I ROP inevitably develop visual field constriction and tend to show significant refractive errors such as high myopia.[10,14–18]

Recently, intravitreal bevacizumab (IVB) injection has emerged as a treatment option, especially for Zone I ROP.[19] In addition to showing a better anatomical outcome than laser treatment alone in Zone I ROP, IVB monotherapy was associated with less refractive errors in Zones I and II ROP.[20–23] However, there are

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concerns about IVB monotherapy for ROP with respect to the proper dose, safety, a persistently avascular peripheral retina, late reactivation, and unestablished follow-up protocol.[24–26] To overcome the disadvantages of conventional laser treatment and IVB monotherapy, combined treatments have been evaluated in several studies of infants with Zones I and II ROP, and they showed good anatomical outcomes.[27–29] Moreover, for the treatment of Zone I ROP, combined IVB and Zone I sparing laser photocoagulation also achieved excellent anatomical outcomes without reactivation or retreatment.[30] Previous studies showed that the area of peripheral retinal vascularization increased over several months after IVB.[19,28] Therefore, if laser photocoagulation is deferred for a period of time and is performed on the peripheral avascular retina after IVB, fewer retinal areas may be subjected to laser photocoagulation, which may result in larger functional areas in the retina. Intravitreal bevacizumab combined with laser treatment may lessen the concerns regarding an uncertain follow-up schedule and late reactivation. Additionally, the refractive outcome may be affected by combined IVB and/or the timing and area of laser treatment. However, few reports have compared anatomical and refractive outcomes in Zone I ROP.

In this study, we investigated the anatomical and refractive outcomes of conventional laser therapy, combined IVB and Zone I sparing laser photocoagulation, and IVB with deferred laser photocoagulation in infants with Type 1 ROP in Zone I, as defined by the Early Treatment for Retinopathy of Prematurity study.

## Methods

This retrospective nonrandomized interventional comparative study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the Samsung Medical Center. Informed consent was obtained from all parents after providing an explanation of the off-label use of bevacizumab and the potential drug-related and injection-related side effects of IVB. After a thorough discussion regarding the expected risks and benefits of treatment, all parents agreed to proceed with the treatment.

The medical records of consecutive preterm infants who were born between November 2004 and December 2013, admitted to the Samsung Medical Center Neonatal Intensive Care Unit and screened for ROP were retrospectively reviewed. The medical records of infants who were referred for the treatment of ROP were also reviewed. Among them, infants who underwent treatment for Type 1 ROP in Zone I in at least 1 eye were included in this analysis (Figure 1). From November 2004 to June 2011, conventional laser treatment was performed (Group I). After the publication of the BEAT-ROP study in 2011, we began IVB as an adjuvant therapy to laser treatment. From July 2011 to October 2012, combined IVB and Zone I sparing laser ablation was performed as the first-line therapy for the treatment of Type 1 ROP in Zone I (Group II) in our center. Although the BEAT-ROP study revealed that IVB monotherapy

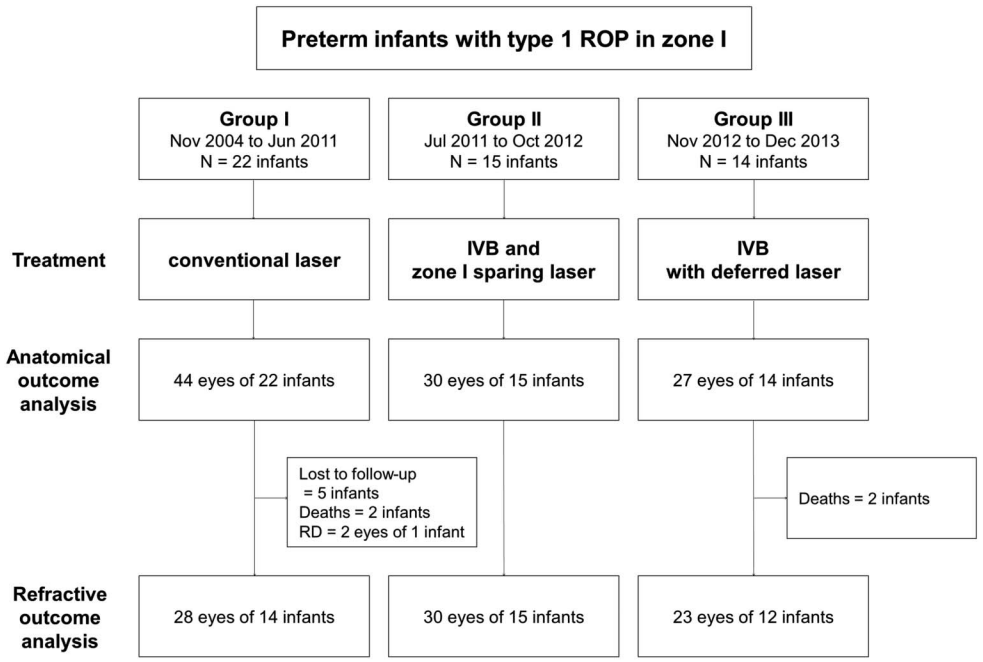


**Fig. 1.** Overall scheme of the study.

was effective for Zone I + ROP, we also performed laser treatment due to concerns about reactivation. Because we observed good anatomical results during this period and because other studies showed that the area of peripheral retinal vascularization increased over several months after IVB,[19,28] we changed the first-line therapy for Type 1 ROP in Zone I to IVB with deferred laser photocoagulation (Group III) in November 2012. We performed laser treatment in all eyes due to concerns about the unestablished follow-up protocol and the possible risk of reactivation. The infants were evaluated for clinical course, treatment interventions, anatomical outcomes, and refractive outcomes.

The screening examination for ROP followed the guidelines proposed by the American Academy of Ophthalmology and Pediatrics and the Association for Pediatric Ophthalmology and Strabismus, with some modifications.[31] The first screening examination was undertaken at 29 weeks to 31 weeks postmenstrual age (PMA), whenever an examination was tolerated by the infants. The treatment criteria were based on Early Treatment for Retinopathy of Prematurity Type 1 disease.

Intravitreal bevacizumab treatments were performed as follows. After dilatation of the pupils with phenylephrine HCl 5 mg/mL and tropicamide 5 mg/mL eye drops, topical anesthesia with proparacaine hydrochloride eye drops was applied. After sterilization with 5% povidone/iodine solution and the insertion of a lid speculum, a dose of 0.25 mg (0.01 mL) of bevacizumab was injected 1 mm to 1.5 mm posterior to the limbus using the 30-gauge needle. In the conventional laser treatment group (Group I), near-confluent laser photocoagulation was performed on the entire area of the avascular retina extending to the ora serrata for 360° (Figure 2A). All laser treatments in this study were performed using an 810-nm laser indirect ophthalmoscope. Infants in Group II received IVB and near-confluent laser photocoagulation on the avascular retina anterior to the margin of Zone I extending to the ora serrata for 360°. The avascular retina posterior to the margin of Zone I was left without laser ablation (Figure 2B). In Group III, IVB preceded laser treatment. While the retina was more vascularized after IVB, the infants underwent fundus examination every week until laser treatment. When the arrest of the anterior progression of the retinal vasculature with a new demarcation line was observed, or the recurrence of arterial tortuosity and venous dilatation was observed, laser photocoagulation was performed on the avascular retina extending to the ora serrata for 360° (Figure 2C). Most laser treatments were performed in the Neonatal Intensive Care Unit bed. However, in Group III, some of the deferred laser treatments were performed in the operating room under general anesthesia.

The fundus was evaluated, and the results were reviewed at each examination after treatment. An unfavorable anatomical outcome was defined as the presence of at least 1 of the following findings: RD, retinal fold, disc dragging, and retrolental tissue obscuring the view of the posterior pole. The presence of vitreous organization, defined as white fibrous-appearing opacification of the vitreous above the vascular/avascular junction, was also reviewed.[32]

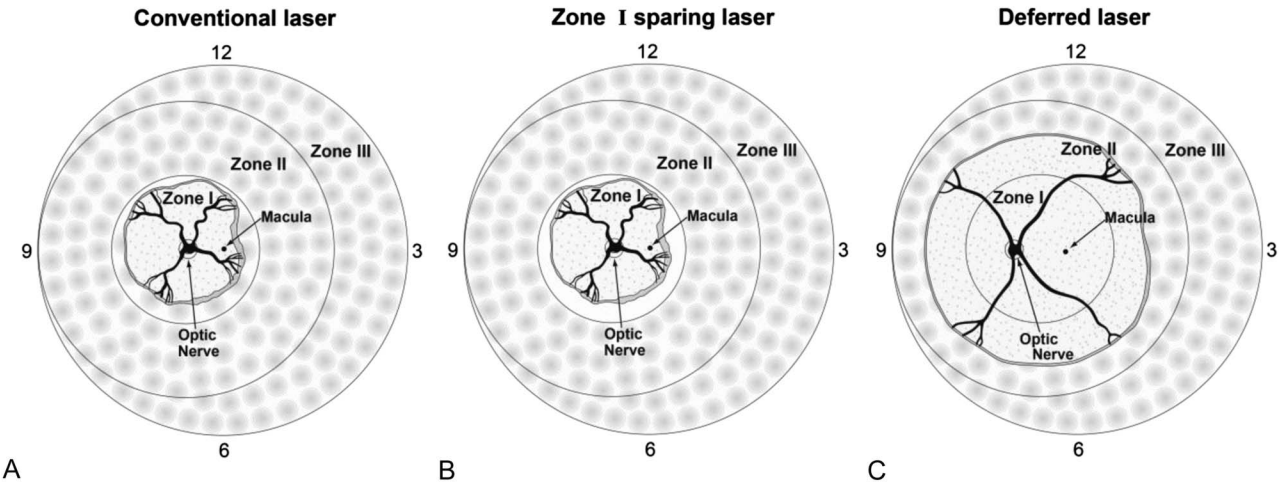


**Fig. 2.** Diagrams showing the 3 methods of laser treatment. The conventional laser treatment, near-confluent laser photocoagulation, was performed on the whole area of the avascular retina extending to the ora serrata in Group I (**A**). Near-confluent laser photocoagulation was performed on the avascular retina anterior to the margin of Zone I extending to the ora serrata in Group II. Avascular retina posterior to the margin of Zone I was left without laser ablation (**B**). After IVB injection, the retina was more vascularized. Then, laser photocoagulation was performed on the avascular retina extending to the ora serrata in Group III (**C**). Gray circles indicate the laser-treated areas.

Infants were evaluated for refractive errors with manual cycloplegic refraction at the age of 12 months to 18 months. The results were recorded as measurements of the spherical, cylinder, degree of astigmatism, and spherical equivalent (spherical plus half of the cylinder power). These refractive errors were divided into 4 categories based on the spherical equivalent as follows: very high myopia (≥−8.0 D), high myopia (<−8.0 to −5.0 D), low myopia (<−5.0 to −1.0 D), and emmetropia (<−1 to 1.0 D).[16,33] Eyes with RD were excluded from the refractive analysis.

Statistical analysis was performed using SPSS for Windows (Version 21.0, SPSS, Inc, Chicago, IL). To compare the three groups, numerical data were analyzed using one-way analysis of variance with Tukey's post hoc test. The categorical data were analyzed using the Chi-square test and Fisher's exact test. The PMAs at which infants received IVB were analyzed by Student's *t*-test. Two-tailed *P* values <0.05 were considered to be statistically significant.

## Results

A total of 101 eyes from 51 consecutive infants with Type 1 ROP in Zone I were included and analyzed. Group I consisted of 44 eyes from 22 infants who received conventional laser treatment only; Group II consisted of 30 eyes from 15 infants who received combined IVB and Zone I sparing laser ablation; and Group III consisted of 27 eyes from 14 infants who underwent IVB with deferred laser photocoagulation. One infant in Group III received IVB with deferred laser treatment in 1 eye only. The fellow eye showed Zone II posterior, Stage 2 ROP without plus disease. Thus, the fellow eye was not included.

The clinical characteristics of the 51 included infants in the 3 groups are shown in Table 1. The mean gestational age of the patients was 24.3 ± 1.1 weeks and the mean birth weight of the patients was 646 ± 143 grams. There was no statistically significant difference in the mean gestational age ($P$ = 0.173), mean birth weight ($P$ = 0.238), and gender ($P$ = 0.813) among the 3 groups.

The mean PMA at the time of receiving laser treatment and IVB in the 3 groups is presented in Table 2. In Group I, the median PMA at the time of receiving laser treatment was 34.4 weeks (range, 30.3–39.8 weeks). The median PMA when infants in Group II underwent Zone I sparing laser treatment was 34.7 weeks (range, 33.7–36.9 weeks). The median PMA when IVB was performed in Group II was 34.7 weeks (range, 33.9–36.9 weeks). The median PMA at the time of receiving IVB in Group III was 34.8 weeks (range, 30.3–37.1 week). The median PMA when deferred laser treatment was performed in Group III was 41.9 weeks (range, 35.3–55.7 weeks). The median time between IVB and deferred laser treatment in Group III was 7.3 weeks (range, 2.9–23.6 weeks). Among the 3 groups, there was no statistically significant difference in the mean time of first treatment ($P$ = 0.425). Among the included patients, 18 eyes from 9 patients in Group I, 12 eyes from 6 patients in Group II, and 12 eyes from 6 patients in Group III showed features of aggressive posterior ROP.

The anatomical outcomes of 101 eyes of the 51 included infants are shown in Table 3. A normal posterior pole was observed in 34 eyes (77.3%) in Group I, 30 eyes (100%) in Group II, and 27 eyes (100%) in Group III ($P$ < 0.001). Unfavorable anatomical outcomes were observed only in Group I. In Group II, the previously avascular Zone I retina was vascularized in all eyes after the treatment.

In Group I, 8 infants were excluded from the refractive analysis. We could not evaluate refractive errors in five infants due to loss to follow-up, two infants due to death, and one infant due to bilateral RD. In Group II, cycloplegic refraction was performed in all included infants. In Group III, two infants died before refractive evaluation. The average durations of follow-up for infants included in the refractive analysis in Groups I, II, and III were 81.1 ± 26.8 months (range, 12–108 months), 38.6 ± 7.3 months (range, 20–47 months), and 25.3 ± 5.3 months (range, 12–33 months), respectively ($P$ < 0.001). The chronological age at the time of cycloplegic refraction and refractive outcomes are presented in Table 4. There was no statistically significant difference in the chronological age at the time of cycloplegic refraction among the 3 groups ($P$ = 0.372). The average refractive errors (spherical equivalent) of patients at 12 months to 18 months of age in Groups I, II, and III were −4.62 ± 4.00 D (range, −13.5 to 1.0 D), −5.53 ± 2.21 D (range, −10.0 to −1.8 D), and −1.40 ± +2.19 D (range, −7.0 to 1.0 D), respectively ($P$ < 0.001). The average levels of astigmatism in infants of the 3 groups were similar: 0.88 ± 0.87 D (range, 0.0–2.8 D), 0.65 ± 0.83 D (range, 0.0–2.0 D), and 0.85 ± 0.61 D (range, 0.0–2.0 D) in Groups I, II, and III, respectively ($P$ = 0.503).

Figure 3 shows the distribution of refractive error among the 3 groups. High myopia (<−8.0 to −5.0 D) was observed in 7 eyes (25.0%) in Group I, 12 eyes (40.0%) in Group II, and 3 eyes (13.0%) in Group III ($P$ = 0.087). Very high myopia (≥−8.0 D) developed in 6 eyes (21.4%) in Group I, in 6 eyes (20.0%) in Group II, and in none of the eyes in Group III ($P$ = 0.034). The proportion of emmetropia (<−1 to 1.0 D)

Table 1. Demographic and Clinical Characteristics of Infants Recruited Into the Study

| | Group I Laser Only (n = 22) | Group II Laser + IVB (n = 15) | Group III IVB + Deferred Laser (n = 14) | *P* |
|---|---|---|---|---|
| GA, mean ± SD (range) | 24.6 ± 0.9 (22–26) | 24.2 ± 1.0 (22–26) | 23.9 ± 1.5 (21–26) | 0.173* |
| Gender, number of males (%) | 14 (64.0) | 8 (53.0) | 8 (57.0) | 0.813† |
| Birth weight, mean ± SD (range) | 685.3 ± 143.1 (370–1,104) | 616.0 ± 113.6 (460–900) | 616.4 ± 165.8 (400–960) | 0.238* |
| SGA number (%) | 2 (9.1) | 2 (13.3) | 1 (7.1) | 1.000† |
| AGA number (%) | 19 (86.4) | 13 (86.7) | 13 (92.9) | 1.000† |
| Number of multiple births (%) | | | | |
| Single | 13 (59.1) | 4 (26.7) | 7 (50.0) | 0.074† |
| Twin | 9 (40.9) | 8 (53.3) | 7 (50.0) | |
| Triplet | 0 (0) | 3 (20.0) | 0 (0) | |
| Apgar score | | | | |
| 1 minute, mean ± SD | 4.1 ± 2.0 | 5.3 ± 1.3 | 4.1 ± 1.3 | 0.074* |
| 5 minutes, mean ± SD | 6.5 ± 2.2 | 6.8 ± 1.3 | 6.2 ± 1.8 | 0.709* |
| Number of cases of PDA ligation (%) | 13 (59.1) | 6 (40.0) | 0 (0) | 0.001† |
| Number of cases with IVH (%) | | | | |
| None | 8 (36.4) | 6 (40.0) | 2 (14.3) | 0.016† |
| Grade I–II | 4 (18.2) | 7 (46.7) | 10 (71.4) | |
| Grade III–IV | 10 (45.5) | 2 (13.3) | 2 (14.3) | |
| Number of cases with BPD ≥ moderate (%) | 12 (54.5) | 11 (73.3) | 12 (85.7) | 0.138† |
| Number of cases that underwent NEC operation (%) | 4 (18.2) | 1 (6.7) | 3 (21.4) | 0.624† |
| Culture-proven sepsis number (%) | 3 (13.6) | 3 (20.0) | 7 (50.0) | 0.054† |
| Number of cases with surfactant ≥2 (%) | 10 (45.5) | 4 (26.7) | 2 (14.3) | 0.138† |
| Transfusion, mean ± SD | 8.7 ± 11.2 | 5.9 ± 2.5 | 6.6 ± 5.6 | 0.563* |
| $O_2$ therapy, mean ± SD (days) | 106.8 ± 63.6 | 81.1 ± 19.9 | 95.7 ± 60.3 | 0.366* |
| Mechanical ventilation, mean ± SD (days) | 52.2 ± 63.5 | 41.4 ± 19.3 | 65.1 ± 49.1 | 0.453* |
| Number of cases with mechanical ventilation ≥30 days (%) | 15 (68.2) | 11 (73.3) | 12 (85.7) | 0.559* |

*One-way analysis of variance.
†Fisher's exact test.
AGA, appropriate for gestational age; BPD, bronchopulmonary dysplasia; GA, gestational age; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; SGA, small for gestational age.

was the highest in Group III: 8 eyes (28.6%) in Group I, none of the eyes in Group II, and 11 eyes (47.8%) in Group III showed emmetropia ($P < 0.001$).

## Discussion

In this study, we compared the anatomical and refractive outcomes in consecutive patients with Type 1 ROP in Zone I who were treated with the following 3 different strategies: conventional laser photocoagulation, combined IVB and Zone I sparing laser therapy, and IVB with deferred laser treatment. Intravitreal bevacizumab with both concomitant laser and deferred laser therapy showed a significantly better anatomical outcome than conventional laser therapy alone. Moreover, IVB with deferred laser treatment resulted in less myopic refractive error. Therefore, IVB with deferred laser treatment showed the best outcome among the 3 treatment methods for Zone I ROP.

The anatomical outcome of Zone I ROP has been reported to be poor compared with that of Zone II ROP. The incidence of RD was reported to range from 18.2% to 70.8% in spite of laser treatment.[10,12,13] The Early Treatment for Retinopathy of Prematurity study[34] reported that 27.8% of eyes with Zone I

Table 2. The PMAs at the Time of Receiving Laser Treatment or IVB Injection

| | Group I Laser Only (n = 44 Eyes) | Group II Laser + IVB (n = 30 Eyes) | Group III IVB + Deferred Laser (n = 27 Eyes) | *P* |
|---|---|---|---|---|
| Laser treatment | | | | |
| PMA (weeks) | 35.1 (34.4) | 35.0 (34.7) | 43.0 (41.9) | NA |
| Mean (median) [range] | [30.3–39.8] | [33.7–36.9] | [35.3–55.7] | |
| IVB | | | | |
| PMA (weeks) | NA | 34.9 (34.7) | 34.3 (34.8) | NA |
| Mean (median) [range] | | [33.9–36.9] | [30.3–37.1] | |
| Time between IVB and laser treatment (weeks) | | | | |
| Mean (median) [range] | NA | 0.2 (0.0) [0.0–1.3] | 8.7 (7.3) [2.9–23.6] | NA |
| Time of first treatment | | | | |
| PMA (weeks) | 35.1 (34.4) | 34.9 (34.6) | 34.3 (34.8) | 0.425* |
| Mean (median) [range] | [30.3–39.8] | [33.7–36.9] | [30.3–37.1] | |

*One-way analysis of variance.
NA, not applicable.

ROP showed an unfavorable outcome after laser treatment, and the BEAT-ROP study[19] reported that 18 of 33 eyes (54.5%) with Zone I ROP showed macular dragging or RD after laser treatment alone. Previous studies with good outcomes after laser monotherapy for Zone I ROP showed that multiple sessions are often necessary.[34–36] In this study, for all infants of the 3 groups, only 1 session of laser treatment was performed. This might have affected the anatomical outcome, especially in Group I. However, the frequency of unfavorable anatomical outcome (22.7%) in Group I did not seem to be higher than values reported in previous studies on laser monotherapy for Zone I ROP. Recently, several reports showed a good anatomical outcome after IVB monotherapy for Zone I ROP. However, the reactivation of ROP has been reported even as late as 69 weeks PMA after IVB.[26] In addition, there have been concerns about IVB in terms of ocular and systemic safety and proper dosage. Combined laser treatment may minimize the concern of late recurrence. We previously found that IVB and Zone I sparing laser treatment for Zone I ROP showed no RD, even with the lowest dose (0.01 mL) of IVB ever reported.[30] Moreover, there was no reactivation or need for retreatment, even when areas of the retina in Zone I were left unlasered at the time of treatment.[30] In this study, we analyzed a large number of patients who received IVB with Zone I sparing laser treatment, and additionally included patients who received IVB with deferred laser. As a whole, all 57 eyes with combined IVB treatment (Groups II and III) showed excellent anatomical outcomes without reactivation or retreatment. Moreover, with IVB and deferred laser treatment, photocoagulation of smaller avascular retinal areas can be performed compared with conventional laser treatment or IVB with Zone I sparing laser therapy. Therefore, IVB with deferred laser treatment may preserve more of the visual field than the other 2 methods.

Zone I ROP is associated with high refractive errors such as high myopia, which may be one of the causes of amblyopia. The Early Treatment for Retinopathy of Prematurity study showed that more than 40% of eyes with Zone I ROP showed high myopia at the age of 4 years to 6 years, which was higher than that in eyes with Zone II ROP.[33] Several studies showed less myopia in eyes treated with IVB monotherapy than in eyes with conventional laser or combined IVB + laser in

Table 3. Anatomical Outcomes of the 101 Included Eyes in the 3 Groups

| Number of Eyes (%) | Group I Laser Only (n = 44 Eyes) | Group II Laser + IVB (n = 30 Eyes) | Group III IVB + Deferred Laser (n = 27 Eyes) | *P* |
|---|---|---|---|---|
| Normal posterior pole | 34 (77.3) | 30 (100) | 27 (100) | <0.001* |
| Unfavorable outcome | 10 (22.7) | 0 (0) | 0 (0) | |
| Retinal fold | 2 (4.5) | 0 (0) | 0 (0) | |
| Disc dragging | 3 (6.8) | 0 (0) | 0 (0) | |
| Retrolental tissue obscuring the view of the posterior pole | 1 (2.3) | 0 (0) | 0 (0) | |
| Retinal detachment | 4 (9.1) | 0 (0) | 0 (0) | |

*Fisher's exact test.

Table 4. Comparisons of Ages at the Time of Cycloplegic Refraction and Refractive Errors Among the Three Groups

| | Group I Laser Only (n = 28 Eyes) | Group II Laser + IVB (n = 30 Eyes) | Group III IVB + Deferred Laser (n = 23 Eyes) | *P* |
|---|---|---|---|---|
| Chronological age at the time of CR (weeks) | | | | |
| Mean ± SD | 64.0 ± 12.9 | 62.3 ± 10.2 | 59.1 ± 12.7 | 0.372* |
| Median | 64.8 | 59.7 | 54.1 | |
| Range | 47.3–88.0 | 52.6–82.4 | 46.4–81.1 | |
| SE (diopters) | | | | |
| Mean ± SD | −4.62 ± 4.00 | −5.53 ± 2.21 | −1.40 ± 2.19 | <0.00bn1* |
| Median | −4.44 | −5.50 | −1.25 | |
| Range | −13.5–1.0 | −10.0 to −1.8 | −7.0–1.0 | |
| Number of eyes with low myopia (%) | 7 (25.0) | 12 (40.0) | 9 (39.1) | 0.420† |
| Number of eyes with high myopia (%) | 7 (25.0) | 12 (40.0) | 3 (13.0) | 0.087† |
| Number of eyes with very high myopia (%) | 6 (21.4) | 6 (20.0) | 0 (0.0) | 0.034‡ |
| Number of eyes with emmetropia (%) | 8 (28.6) | 0 (0.0) | 11 (47.8) | <0.001† |
| Astigmatism (diopters) | | | | |
| Mean ± SD | 0.88 ± 0.87 | 0.65 ± 0.83 | 0.85 ± 0.61 | 0.503* |
| Median | 0.75 | 0.00 | 1.00 | |
| Range | 0.0–2.8 | 0.0–2.0 | 0.0–2.0 | |

*One-way analysis of variance.
†Chi-square test.
‡Fisher's exact test.
CR, cycloplegic refraction; SE, spherical equivalent.

Zone I and II ROP.[20–23] In our study on Zone I ROP, IVB with deferred laser treatment showed low refractive error. Only 13.0% of the eyes in the IVB with deferred laser therapy group showed a refractive error of −5.0 D or more. Compared with IVB monotherapy, one of the major concerns of combined IVB + laser treatment may be the high refractive error. Although no direct comparison with IVB monotherapy can be made, this study suggests that IVB with deferred laser treatment can be a good treatment method to reduce refractive error in eyes with Zone I ROP. The factors that contribute to the lower degree of myopia in eyes treated with IVB with deferred laser therapy are not clear. The time and extent of laser treatment might influence the degree of refractive error.

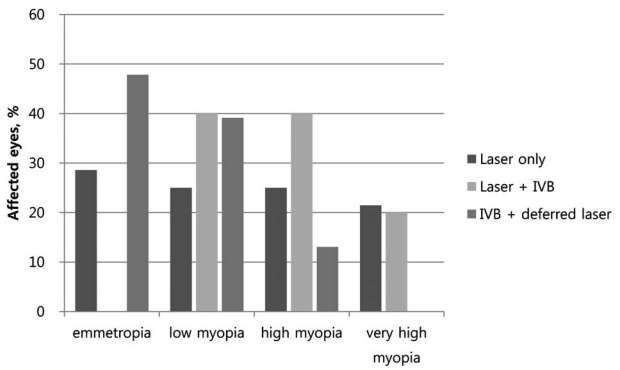


**Fig. 3.** Distribution of refractive errors among the 3 groups. Distribution of spherical equivalent refractive error among the 3 groups at the age of 12 months to 18 months. Each category is defined as follows: emmetropia (<−1 to 1.0 D), low myopia (<−5.0 to −1.0 D), high myopia (<−8.0 to −5.0 D), and very high myopia (≥−8.0 D).

This study has several limitations including its retrospective and nonrandomized nature. Its major limitation is that it is a historical comparison, not a simultaneous comparison, as this may be a significant source of confounding and bias. There are temporal trends such as protocols for oxygen treatment and management of sepsis, nutrition, and patent ductus arteriosus, which might influence not only the development but also the behavior of ROP, which would affect the treatment outcomes. In this study, several risk factors such as patent ductus arteriosus, intraventricular hemorrhage, and sepsis were significantly different among the three groups. A prospective study that compares the anatomical and refractive outcomes between combined IVB and laser treatment, laser monotherapy, and IVB monotherapy is necessary. Furthermore, in this study, screening exams and treatments were not performed by physicians with similar levels of experience. Even among experts, there is significant disagreement regarding the identification of Zone I and plus disease.[37,38] These issues and the lack of clear treatment protocols are the major limitations of this study. As this is a historical comparison, the total lengths of follow-up for each group

were significantly different. Additionally, in the refractive analysis, 8 infants were excluded from the analysis, which could also be one of the limitations. In addition, we could not compare our results to a group who received IVB therapy alone and wide-field fundus photography was not performed, which limited the evaluation of the extent of revascularization after IVB. Although this is a retrospective study, this case series included consecutive patients with Zone I ROP over a 10-year period. Moreover, to the best of our knowledge, this is the largest series of patients with Zone I ROP treated with IVB, and the first comparative study between IVB with concomitant laser or deferred laser therapy. Therefore, our study may provide valuable information for making a decision regarding the treatment method in Zone I ROP.

Several studies reported good anatomic results after IVB monotherapy in Zone I ROP.[19,21,39] However, in this study, we performed laser photocoagulation in all eyes with Zone I ROP. Although the incidence of recurrence after IVB monotherapy is not high,[23] the reactivation of ROP has been reported, even at 35 weeks postinjection.[26] Thus, at least for now, combined laser treatment in all eyes after IVB may be a safe approach with less reactivation and less frequent examinations. However, this approach may result in overtreatment. Therefore, further studies are warranted to select the eyes with Zone I ROP in which IVB alone is effective and to establish a protocol for monitoring progress after IVB monotherapy.

In conclusion, in Type 1 ROP in Zone I, IVB with concomitant or deferred laser therapy may result in more favorable anatomic outcomes than conventional laser treatment alone. Moreover, IVB with deferred laser treatment resulted in less myopic refractive error. The advantages of this treatment method may include a more favorable anatomic outcome, a lower possibility of reactivation, less frequent examinations after treatment, the preservation of larger unlasered retinal areas, and less myopia. Further, well-controlled prospective studies are warranted to confirm our findings.

**Key words:** bevacizumab, laser photocoagulation, refractive outcome, retinopathy of prematurity.

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