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Ten-year outcomes after initial management with laser photocoagulation versus intravitreal bevacizumab injection in a pair of identical twins with aggressive posterior retinopathy of prematurity

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ABSTRACT

Purpose: To evaluate the long-term clinical outcomes after initial management with retinal laser photocoagulation (RLP) versus intravitreal bevacizumab (IVB) injection in identical twins with zone I aggressive posterior retinopathy of prematurity (AP-ROP).

Observations: Identical female twins were born at a gestational age of 28 2/7 weeks, weighing 970 g and 1020 g. The twins were diagnosed with bilateral AP-ROP, referred to a different hospital due to unavilability of a neonatal intensive care unitand received different initial treatments. At a postmenstrual age of 32 6/7 weeks, the first-born infant underwent bilateral IVB (0.313 mg) injection, whereas the second-born infant received bilateral laser photocoagulation on the same day. To treat recurrence, the first-born infant underwent additional bilateral IVB reinjection at 10 weeks post-treatment, while the second-born infant underwent combined bilateral laser photocoagulation and IVB injection at 2 weeks post-treatment.

After 10 years, the first-born infant's best corrected visual acuities (BCVAs) of the right and left eyes were 20/20 and 20/50, respectively. Both eyes showed complete retinal vascularization of the peripheral retina and an anatomically normal foveal contour on swept-source optical coherence tomography (SS-OCT). However, the second-born infant's BCVAs of the right and left eyes were 20/50 and 1-m finger-counting, respectively. Both eyes of the second-born infant showed panretinal chorioretinal atrophy due to laser scars, a flattened foveal contour with thin epiretinal membrane in the right eye, and loss of foveal curvature in the left eye on SS-OCT images, 10 years after the initial treatment. Moreover, severe myopia and astigmatism were observed in both eyes of the second-born infant, compared with those of the first-born infant during follow-up.

Conclusion and importance: These cases involving identical twins indicated that the effect of initial IVB injection for AP-ROP was superior to that of initial RLP in terms of functional and anatomical outcomes during a 10-year follow-up.

1. Introduction

Retinopathy of prematurity (ROP) is a leading cause of visual morbidity worldwide.[1] Although the Early Treatment for Retinopathy of Prematurity Cooperative Group reported that unfavorable clinical outcomes were reduced by performing retinal laser photocoagulation (RLP) at pre-threshold retinopathy, rather than at threshold retinopathy, severe vision loss due to serious complications, including retinal detachment, retinal folds, and retrolental hyperplasia, occurred in about 10% of patients.[2] A severe form of ROP, including Rush-type ROP and type II ROP, was classified as aggressive posterior retinopathy of prematurity (AP-ROP) in 2005.[3] AP-ROP usually occurs in premature infants with gestational age (GA) < 28 weeks and low birth weight (<1000 g).[4] Since AP-ROP is located more posteriorly and progresses rapidly, the prognosis of AP-ROP has been poor, despite early intervention.[5] Given that vascular endothelial growth factor (VEGF) dysregulation has been associated with the pathogenesis of ROP, anti-VEGF agents, mostly bevacizumab (Avastin, Genentech, San Francisco, CA, USA), have been used off-label in several studies.[6–9]

While RLP is associated with ocular complications, such as visual

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field defects due to photoreceptor damage and development of high myopia, intravitreal bevacizumab (IVB) injection is less invasive and can be performed under topical anesthesia.[2,8,10] Although the Bevacizumab Eliminates the Angiogenic Threat of Retinopathy (Beat-ROP) study showed significant benefits of IVB, as compared with RLP, several comparative studies of IVB and RLP did not confirm its superiority.[8,11–13]

Here, we report the 10-year clinical outcomes of identical twins who received different initial treatments, either IVB or RLP.

2. Case report

Identical female twins with a GA of 28 2/7 weeks at birth were born at a local general hospital. The body weight of the first-born and second-born infants were 970 g and 1002 g, respectively. The first-born infant's Apgar scores were 5 at 1 minute and 6 at 5 minutes, and the second-born infant's Apgar scores were 5 at 1 minute and 7 at 5 minutes. Both twins were diagnosed with bronchopulmonary dysplasia and received synchronized intermittent mandatory ventilation treatment for 30 days. On ROP screening at the postmenstrual age (PMA) of 32 3/7 weeks, both eyes of both twins were diagnosed with "plus disease," with dilatation and tortuosity of the major posterior vessels. A ridge with extraretinal fibrovascular proliferation with a circle in zone I without involving the fovea and scattered retinal hemorrhages were observed in both eyes. As the fundus features of stage 3 ROP in zone I were very similar between both twins, AP-ROP in both eyes of both twins was confirmed by a retinal specialist at the local hospital. For emergency treatment, the first-born infant was admitted to our hospital, whereas the second-born infant was transferred to another hospital because of the unavailability of a neonatal intensive care unit.

At PMA 32 6/7 weeks, the first-born infant received bilateral IVB with a dose of 0.313 mg/0.015 mL. IVB injection was performed under topical anesthesia with 5% proparacaine in the operating room. Written informed consent for off-label use of IVB was obtained from the patient's legal guardian. A sterile 30-gauge needle was inserted at 1-mm posterior to the limbus, after povidone-iodine sterilization. Topical moxifloxacin was administered over a period of 7 days. The vascular tortuosity and extraretinal fibrovascular proliferation regressed markedly and retinal vessels grew up to zone II at 3-weeks post-treatment. Since both the fundi of the first-born infant showed recurrence, such as increased vascular tortuosity and newly developed focal retinal hemorrhages, bilateral IVB (0.313 mg) reinjection was performed 10 weeks after the initial treatment. The ROP gradually regressed after second IVB injection. Complete retinal vascularization was observed 6 months after the initial IVB, after which the infant was followed up every 6 months. Ten years after the initial IVB in the first-born infant, the best corrected visual acuity (BCVA) of the right and left eye was 20/20 and 20/50, respectively. The spherical equivalent refractive errors of the right eye and left eye were +2.75 D and −5.625 D, respectively. The amblyopia and astigmatism of the left eye was treated with eye patch for 4 years and wore glasses during last 6 years. The axial lengths of the right and left eyes were 19.93 mm and 22.69 mm, respectively, at the 10-year follow-up. Additionally, wide-field fundus photos of both eyes showed complete retinal vascularization of the peripheral retina and swept-source optical coherence tomography (SS-OCT) image revealed a normal foveal contour (Fig. 1). The internal anterior chamber depths of the right and left eyes were 2.90 mm and 3.01 mm, respectively. The flat/steep corneal dioptric values of the right and left eyes were 44.4/46.8 D and 43.6/47.3 D, respectively, as assessed using a Scheimpflug rotating camera (Pentacam HR, Oculus; Wetzlar, Germany) (Fig. 2).

On the other hand, both eyes of the second-born infant received initial bilateral RLP, 1800 spots to the right eye and 2000 spots to the left eye with a power intensity of 340 mW via a laser indirect ophthalmoscope (VISULAS 532s, Carl Zeiss Meditec, Dublin, CA, USA) under general anesthesia at PMA 32 6/7 weeks, on the same day as the first-born infant, according to the retinal specialist's discretion at the other university hospital. Based on fundus findings, Stage 3 ROP with plus disease in Zone I, indicating AP-ROP in both eyes, was also confirmed. Since the second-born infant showed recurrence, including increased vascular tortuosity and retinal hemorrhage, at 2 weeks post-treatment, secondary bilateral RLP combined with IVB injection (0.675 mg/0.03 mL) was performed. An additional 1400 spots to the right eye and 1300 spots to the left eye were irradiated with a power intensity of 360–460 mW. Two days after this additional RLP, the infant was treated with vancomycin for a week because of a methicillin-resistant *Staphylococcus epidermidis* (MRSE) infection and subsequently recovered well without sequelae. At 1 year post-treatment, the second-born infant was transferred to our hospital for a regular check-up. Ten years after the initial RLP, the BCVA of the right and left eye was 20/50 and 1-m finger counting, respectively. The spherical equivalent refractive errors of the right and the left eyes were −17.0 D and −15.50 D, respectively. The axial lengths were 24.02 mm in the right eye and 22.60 mm in left eye. To treat severe myopia and astigmatism, the second-born infant has been prescribed eyeglasses for the last 6 years. The wide-field fundus photos of both eyes showed pan-retinal chorioretinal laser scaring in both eyes. SS-OCT images showed a flattened foveal contour in the right eye and a thin retina with a loss of foveal curvature in the left eye (Fig. 3). The internal anterior chamber depths of the right and left eyes were 2.13 mm and 2.08 mm, respectively. The flat/steep corneal dioptric values of the right and left eye were 43.9/48.3D and 44.2/49.0D,

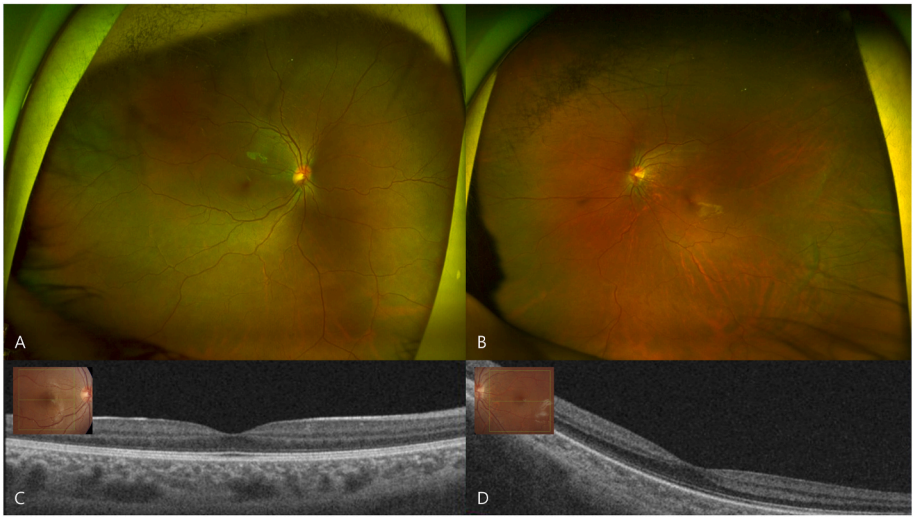

Fig. 1. The first-born infant was treated with bilateral Intravitreal bevacizumab (IVB) injections twice. (A) Wide-field fundus photography of the right eye at 10 years after the initial IVB treatment shows complete retinal vascularization of the peripheral retina. (B) Fundus photography of the left eye shows complete vascularization with a tigroid fundus. (C) Swept-source optical coherence tomography (SS-OCT) image of the right eye shows a normal foveal contour at 10 years. (D) The SS-OCT image of the left eye shows a normal foveal curvature with an ellipsoid zone.

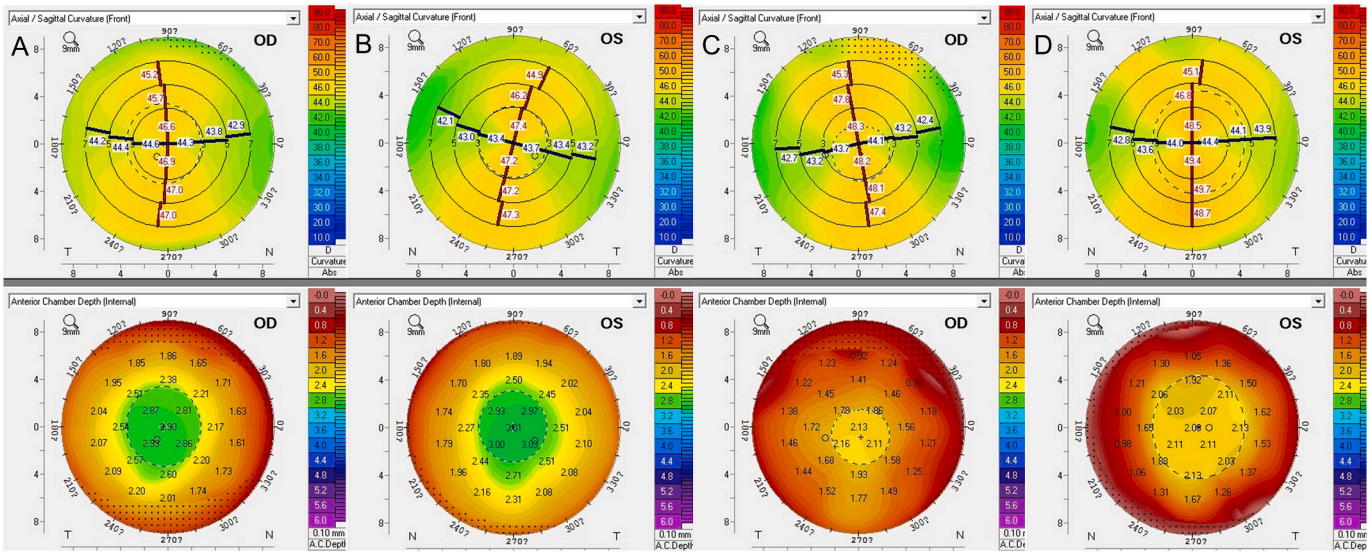

Fig. 2. Axial/sagittal curvature map (top) and internal anterior chamber depth (ACD) map (bottom) at post-treatment 10 years. (A) The flat/steep corneal dioptric values were 44.4/46.8 D, and the internal ACD was 2.90 mm in the right eye of the first-born infant. (B) The flat/steep corneal dioptric values were 43.6/47.3 D and the internal ACD was 3.01 mm in the left eye of the first-born infant. (C) The flat/steep corneal dioptric values were 43.9/48.3 D and the internal ACD was 2.13 mm in the right eye of the-second-born infant. (D) The flat/steep corneal dioptric values were 44.2/49.0 D and the internal ACD was 2.08 mm in the left eye of the second-born infant.

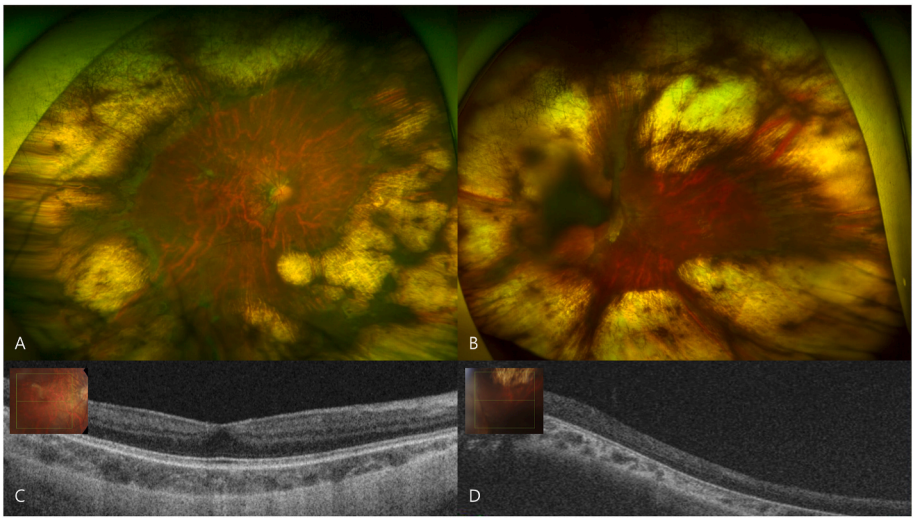

Fig. 3. The second-born infant was first treated with bilateral retinal laser photocoagulation (RLP). Additional bilateral RLPs combined with bilateral intravitreal bevacizumab (IVB) injections were performed at 2 weeks after the initial RLP. (A) Wide-field fundus photography of the right eye at 10 years after the initial RLP shows a tigroid fundus with panretinal chorioretinal atrophy due to laser scars. (B) Fundus photography of the left eye shows panretinal chorioretinal atrophy and very thin major temporal arcade vessels at 10 years post-treatment. A posterior polar cataract obscures the nasal retina partly. (C) A swept-source optical coherence tomography (SS-OCT) image of the right eye shows a flattened foveal contour with a thin epiretinal membrane. (D) The SS-OCT image of the left eye shows a very thin retina and loss of the foveal curvature.

respectively. Therefore, the second-born infant had a shallower anterior chamber and steeper cornea than the first-born infant.

In addition, the duration of oxygen therapy in the first- and second-born infant after the initial treatment differed by only 2 days: 54 and 52 days, respectively.

3. Discussion

Although multiple sessions of RLP for zone 1 AP-ROP showed good anatomical results as compared to a single session of RLP, most previously reported AP-ROP cases showed a poor prognosis due to rapid disease progression.[3,13] Currently, anti-VEGF agents are widely used for treating ROP because of their powerful regressive effects on the vascular proliferation of ROP.[6,7] However, the choice of optimal treatment between RLP and anti-VEGF agents remains controversial. In this report, we demonstrated that initial IVB injection rather than initial RLP was more effective for treating AP-ROP in identical twins who had very similar clinical conditions.

In a previous study, infants who received anti-VEGF as an initial treatment required more frequent hospital visits and long-term follow-up examinations than those who underwent RLP because of the delayed vascularization and recurrence of ROP after anti-VEGF treatment.[14] In addition, concerns regarding the neurological development in premature infants treated with initial anti-VEGF agents has increased because the incidence rate of periventricular leukomalacia (PVL), an underlying condition for the development of cerebral palsy, peaks between PMA 23–32 weeks.[15] However, there was no difference in neurodevelopmental adverse outcomes between the RLP and anti-VEGF-treated groups in a recent study.[16] In the present study, although the first-born infant received additional IVB, no developmental abnormalities were observed during the 10-year follow-up. The second-born infant, who received additional RLP combined with IVB, also showed no developmental abnormalities. In both twins, no abnormalities in neurological and brain development were observed by the pediatrician during the 10year follow-up. Since both infants eventually received IVB, the superiority of IVB over RLP cannot by concluded from

their normal neurodevelopmental outcomes.

In a recent case series report, salvage therapy with IVB for recurrence after initial RLP achieved favorable anatomical and functional outcomes. While initial RLP rather than initial IVB was performed to avoid the potential risk of VEGF suppression at early developmental stages, the measurable visual acuity in all 8 infants in the series ranged from 20/1400 to 20/260 at 2-years post-treatment.[17] In addition to poor functional outcomes, initial RLP for very premature infants can increase the anesthesia-related morbidity due to their cardiovascular instability.[18]

In the 2.5-year refractive outcomes of the BEAT-ROP clinical trial, the mean spherical equivalent (SE) refractions of eyes treated with anti-VEGF were -1.51 ± 3.42 D, whereas those of eyes that underwent RLP were -8.44 ± 7.57 D.[8] Similarly, the SE refractions of the second-born infant in the present study showed very severe high myopia, as compared to those of the first-born infant. The myopia in ROP is known to be caused by nonaxial factors including a steepened cornea, shallow anterior chamber, and thickened crystalline lens.[19] Besides the higher axial length in the second-born infant, the steepened cornea might have contributed to the higher refractive error in both eyes. The steepened cornea and shallower anterior chamber depth might be due to an arrested state of development in the immature eye.[20,21] Moreover, the development of high myopia after IVB injection has been associated with abnormalities in the anterior segment rather than changes in the axial length.[22] However, we were unable to identify the cause of the difference in the axial lengths between both eyes of the first-born infant in this report. Since ROP treatment by RLP has been reported to cause high myopia in several reports, IVB rather than RLP may be more advantageous, to avoid amblyopia due to high myopia.[23,24] Although the polar type cataract in the left eye of the second-born infant was too small to interrupt the visual axis, it might have been a possible cause of the visual impairment.

While RLP with skipped areas has been shown to cause ROP recurrence,[25] initial RLPs have been applied to cover the avascular retina fully without any skipped areas. Although the second-born infant received additional RLP combined with a double-dose of bilateral IVB, as compared to that of the first-born infant, the left eye of the second-born infant showed very poor visual acuity. Therefore, we speculate that IVB was more effective than RLP at the initial treatment in our cases. Furthermore, since the period for ventilation therapy was similar between twins, ventilation therapy appeared not to have affected the clinical outcomes of twins.

Although the identical twins were similar in birth weight, ROP severity, and the time of initial treatment, it is possible that the clinical course after ROP treatment could have been influenced by different childhood environments during the follow-up period. Since the identical twins were raised in the same household, the influence of environmental factors might be minimal.

4. Conclusion

With a 10-year follow-up, we demonstrate that initial IVB injection rather than initial RLP was more effective for treating AP-ROP in identical twins who had very similar initial clinical conditions.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship contributions

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

None.

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