COMBINED INTRAVITREAL BEVACIZUMAB INJECTION AND ZONE I SPARING LASER PHOTOCOAGULATION IN PATIENTS WITH ZONE I RETINOPATHY OF PREMATURITY

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Purpose: To investigate the anatomical outcome of combined intravitreal bevacizumab injection and Zone I sparing laser ablation in patients with Type 1 retinopathy of prematurity in Zone I.

Methods: The medical records of consecutive 18 eyes of 10 infants, who underwent combined intravitreal bevacizumab (0.25 mg) injection and Zone I sparing laser ablation for the treatment of Type 1 retinopathy of prematurity in Zone I, were retrospectively reviewed. Laser photocoagulation was performed on the avascular retina anterior to the margin of Zone I extending to the ora serrata. Anatomical outcomes including progression to stage 4/5, macular changes, and vitreous organization were reviewed.

Results: The mean gestational age at birth and the birth weight of included patients were 24.0 weeks and 628 g, respectively. The timing of bevacizumab injection ranged from postmenstrual age 33^{+2} to 35 weeks (mean, 34.3 weeks). Postmenstrual age at last follow-up ranged from 74^{+6} to 107^{+1} weeks (mean, 83.6 weeks). All 18 eyes demonstrated prompt regression of neovascular pathology and plus disease without recurrence. Previously avascular Zone I retina was vascularized in all eyes after the treatment. All eyes showed excellent anatomical outcome with intact macula, but one eye showed mild vitreous organization above the vascular/avascular junction.

Conclusion: Combined intravitreal bevacizumab injection and Zone I sparing laser ablation for Type 1 retinopathy of prematurity in Zone I seem to be effective treatment options. Possible advantages include lower dose of anti–vascular endothelial growth factor, less recurrence than monotherapy, and preservation of central visual field.

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Retinopathy of prematurity (ROP) is a leading cause of blindness and visual impairment in children.[1] Although the overall anatomical and visual outcomes have been improved by timely laser treatment, the outcome of Zone I ROP is not always satisfactory.[2] As younger preterm infants are surviving due to advances in neonatal intensive care, more infants are at risk of developing Zone I ROP.[2] The anatomical and visual outcomes of Zone I ROP have been reported to be poor in several studies.[3–6]

Peripheral retinal ablation with conventional laser photocoagulation is a destructive treatment method that damages the majority of cells that produce proangiogenic factors, such as vascular endothelial growth factor (VEGF) in the retina.[7] Thus, laser treatment often causes complications, such as visual field constriction, and does not prevent all cases of visual impairment, especially in cases of Zone I ROP.[3] Intravitreal injection of anti-VEGF agents, which block the action of VEGF, a key factor promoting angiogenesis, is an emerging treatment for ROP. A prospective, randomized controlled clinical trial revealed that intravitreal bevacizumab monotherapy,

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compared with conventional laser therapy, in infants with Stage 3 plus ROP showed a significant benefit for Zone I ROP.[7] However, there are concerns about anti-VEGF treatment for ROP regarding optimal dosage, timing of injection, recurrences, ocular and systemic safety, proper follow-up protocol, and long-term functional outcome.[8–13]

To minimize the possible disadvantage of laser ablation and intravitreal anti-VEGF monotherapy, combined treatments have been pursued in several studies.[14–16] The rationale of the combined treatment is the possible synergistic effect of the blocking action of VEGF by anti-VEGF agents and suppression of further production of proangiogenic factors, such as VEGF by laser ablation. The addition of laser ablation to anti-VEGF treatment might show a reduction in the recurrence rate and decrease in the dose of anti-VEGF as well as achieving good anatomical outcome. Moreover, with Zone I sparing peripheral laser ablation, preservation of more central retina might be achieved. Herein, we investigated the anatomical outcome of combined intravitreal bevacizumab injection and Zone I sparing laser ablation in patients with Type 1 ROP—based on Early Treatment for Retinopathy of Prematurity study—in Zone I.

Methods

The medical records of consecutive preterm infants who were born from April 2011 to December 2011, admitted to the Samsung Medical Center Neonatal Intensive Care Unit, and screened for ROP were retrospectively reviewed. Since July 2011, in our center, for the treatment of Type 1 ROP in Zone I, combined intravitreal bevacizumab injection and Zone I sparing laser ablation have been performed as the first-line therapy. In this study, the medical records of consecutive infants who underwent a combined intravitreal bevacizumab injection and Zone I sparing laser ablation for the treatment of Type 1 ROP in Zone I in at least 1 eye were retrospectively analyzed. The infants were evaluated for clinical courses, treatment interventions, and anatomical 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.[17] 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. Infants with Type 1 ROP in Zone I received intravitreal bevacizumab injections and near-confluent laser photocoagulation on the avascular retina anterior to the margin of Zone I extending to the ora serrata for 360° using an 810 nm laser indirect ophthalmoscope (Figure 1). Avascular retina posterior to the margin of Zone I was left without laser ablation. After dilatation of the pupils with phenylephrine HCl 5 mg/mL and tropicamide 5 mg/mL eye drops, the injections were administered under topical anesthesia with proparacaine hydrochloride eye drops. After sterilization with 5% povidone/iodine solution and 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. After combined treatment, weekly examinations were performed during the first month, and then, monthly examinations were performed for at least 6 months.

Fundus findings at each examination and anatomical outcome including progression to Stage 4/5, retinal fold or dragging, and vitreous organization were reviewed. Vitreous organization was considered to be present when white fibrous-appearing opacification of the vitreous was seen above the vascular/avascular junction.[18]

The 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 explanation of potential drug-related and injection-related side effects of intravitreal bevacizumab injection treatment. After a thorough discussion regarding expected risks and benefits of treatment, all parents agreed to proceed with the combination therapy.

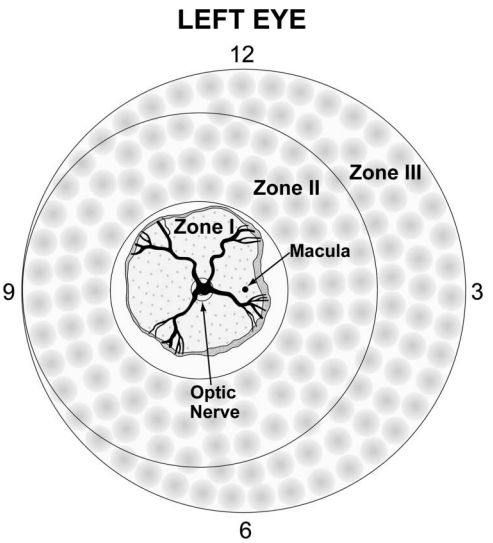

Fig. 1. A diagram showing Zone I sparing laser treatment method. In eyes with Type 1 ROP in Zone I, near-confluent laser photocoagulation was performed on the avascular retina anterior to the margin of Zone I extending to the ora serrata. Avascular retina posterior to the margin of Zone I was left without laser ablation. Gray circles mean laser treated areas.

Results

Medical records of 18 eyes of 10 consecutive infants diagnosed with Type 1 ROP in Zone I were analyzed. The clinical characteristics of 10 included infants receiving combined intravitreal bevacizumab injection and Zone I sparing laser ablation are shown in Table 1. The gestational age at birth of the infants ranged from 23 weeks to 25^{+2} weeks (mean, 24.1 ± 0.78 weeks), and the birth weight varied from 500 g to 760 g (mean, 628.1 ± 73.3 g). Eight babies were from multiple birth pregnancies, and the remainder babies were singlets. All babies showed various comorbidities, as shown in Table 1. The extent of ROP in Zone I ranged from 3-o' to 12-o' clock hours, including 8 eyes for 12-o' clock hours, 2 eyes for 6-o' clock hours, 1 eye for 4-o' clock hours, 5 eyes for 3-o' clock hours, and 2 eyes for 2-o' clock hours (Table 2). There were no eyes with ROP in posterior Zone I, a circular area defined by the radius from the optic disk to the center of the macula.[3,19] The PMAs at treatment are shown in Table 2. In the first 3 cases, laser treatment was carried out 1 day before intravitreal bevacizumab injection. In these cases, there were still plus diseases at the time of intravitreal injection of bevacizumab. After our positive experiences with intravitreal bevacizumab injections, intravitreal bevacizumab injection was administered before or concurrently with laser treatment. In 12 eyes of 7 infants, intravitreal bevacizumab injection was administered before or concurrently with laser treatment. In these cases, the time from bevacizumab injection to laser treatment ranged from 0 day to 8 days (median, 3 days). The mean number of laser spots in 18 eyes was 2053 ± 325 spots per eye. The PMA at last follow-up ranged from 74^{+6} to 107^{+1} weeks (mean, 83.6 weeks; Table 2).

Treatment outcomes of 18 eyes are shown in Table 2. All infants demonstrated prompt regression of neovascular pathology and plus disease within a week from the bevacizumab injection. Vascularization reached Zone II in all eyes after the treatment. One eye showed mild vitreous organization above the vascular/avascular junction. In this eye, after combined bevacizumab and Zone I sparing laser photocoagulation, fibrovascular proliferation was promptly regressed. However, 3 months after the treatment, mild vitreous organization above the vascular/avascular junction of the eye was newly detected. At the last examination at the age of 84 weeks PMA, there was still mild vitreous organization only. No eyes progressed to Stage 4 or 5. During the follow-up period, no recurrence was found, and all infants needed no retreatment. No infants developed preretinal or vitreous hemorrhage, dragging of optic disk or macula, endophthalmitis, and retinal detachment. In all infants, the macula was intact at last examination. There were no systemic adverse events.

Discussion

In this case series, all 18 eyes with Type 1 ROP in Zone I that underwent combined intravitreal bevacizumab injection and Zone I sparing laser ablation showed excellent anatomical outcome. This strategy has two distinct features compared to previously reported treatment methods using bevacizumab. In terms of dose, we injected 0.25 mg/0.01 mL of bevacizumab, the lowest effective dose that has ever been reported. The dose of intravitreal bevacizumab monotherapy in previous reports, which showed effective regression of ROP, ranged from 0.40 mg to 0.75 mg, about a half the adult dose.[7,20–24] Because even a total of 0.50 mg of intravitreal bevacizumab was reported to reduce the serum level of VEGF significantly, consideration should be given to decreasing the systemic exposure by injecting a lower effective

Table 1. Clinical Characteristics of 10 Included Infants Receiving Intravitreal Bevacizumab Injection and Laser Ablation

Case No.	Gestational Age (Weeks)	Birth Weight (g)	Multiple Birth	BPD Grading	IVH Grading	PDA Ligation	Duration of Mechanical Ventilation (Days)
1	24^{+5}	760	Singlet	Moderate	2	–	45
2	23	610	Triplet	Moderate	1	+	53
3	23	560	Triplet	Moderate	2	+	87
4	23	500	Triplet	Moderate	3	+	53
5	24^{+1}	641	Twin	Moderate	0	–	19
6	25^{+2}	670	Singlet	Moderate	0	+	25
7	24	650	Twin	Moderate	3	+	29
8	24	630	Twin	Moderate	0	+	26
9	24^{+5}	570	Twin	Mild	0	–	36
10	24^{+5}	690	Twin	Severe	0	–	6
Mean (SD)	24.1 (0.78)	628.1 (73.3)					37.9 (22.8)

BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus.

Table 2. Treatment Outcomes of 18 Eyes of 10 Included Infants Receiving Intravitreal Bevacizumab Injection and Zone I Sparing Laser Photocoagulation

Case No.	Eye	Stage*	Extent in Zone I (Clock Hours)	PMA at Bevacizumab Injection (Weeks)	PMA at Laser Ablation (Weeks)	PMA at Last Follow-Up (Weeks)	Time to Resolution of Plus Disease After Intravitreal Bevacizumab	Vitreous Organization	Macula at Last Examination	Reactivation or Retreatment
1	Right	3+	12	34^{+5}	34^{+4}	107^{+1}	<1 Week	—	Intact	—
	Left	3+	12				<1 Week	—	Intact	—
2	Right	2+	12	34^{+3}	34^{+2}	82^{+5}	<1 Week	—	Intact	—
	Left	2+	12				<1 Week	—	Intact	—
3	Right	2+	12	34	33^{+6}	82^{+5}	<1 Week	—	Intact	—
	Left	2+	12				<1 Week	—	Intact	—
4	Right	2+	12	34^{+3}	34^{+5}	82^{+5}	<1 Week	—	Intact	—
	Left	2+	12				<1 Week	—	Intact	—
5	Right	2+	6	33^{+2}	33^{+5}	74^{+6}	<1 Week	—	Intact	—
	Left	2+	6				<1 Week	—	Intact	—
6	Right	3+	3	35	35^{+3}	80	<1 Week	—	Intact	—
	Left	3+	4				<1 Week	—	Intact	—
7	Right	3+	3	34^{+4}	35^{+5}	84	<1 Week	—	Intact	—
8	Right	3+	2	34^{+4}	34^{+4}	84	<1 Week	—	Intact	—
	Left	3+	2				<1 Week	+, Mild	Intact	—
9	Right	2+	3	34	34^{+3}	78^{+6}	<1 Week	—	Intact	—
	Left	2+	3				<1 Week	—	Intact	—
10	Left	2+	3	34	35	78^{+6}	<1 Week	—	Intact	—
Mean (SD)	—	—	7.3	34.3 (0.49)	34.6 (0.63)	83.6 (8.76)	—	—	—	—

*"+" means plus disease.

dose.[10] In this study, 0.25 mg of intravitreal bevacizumab promptly regressed plus sign and showed a favorable outcome. Second, near-confluent laser photocoagulation was performed on the avascular retina anterior to the margin of Zone I, thus sparing central retina. With conventional laser treatment for Zone I ROP, laser scars are very close to macula, which may significantly constrict nasal visual field. Thus, this combined laser treatment strategy with bevacizumab may be a good treatment option for Zone I ROP in terms of preservation of central visual field as well as favorable anatomical outcome.

Recently, Hu et al[13] reported that effect of intravitreal bevacizumab monotherapy might be transient. They described 17 eyes with ROP that developed progression of disease despite intravitreal bevacizumab. In their case series, mean age at treatment-requiring recurrence was 49.3 weeks PMA, ranging from 37 weeks to 69 weeks PMA, and the mean time between initial treatment and treatment-requiring recurrence was 14.4 weeks, with a maximum of 35 weeks. They also reported that all 4 eyes that received a second injection of bevacizumab for recurrence received laser photocoagulation in the end and no eye that received laser photocoagulation progressed to retinal detachment. In our case series with at least 41 weeks of follow-up after the treatment, no recurrence was found. Therefore, in terms of reactivation, combined intravitreal bevacizumab injection and laser photocoagulation may have benefit compared with bevacizumab monotherapy.

The anatomical outcomes of Zone I ROP have been reported to be poor in several studies. Kychenthal et al[3] reported treatment outcomes of 57 consecutive eyes with Zone I ROP treated with pure laser ablation. Seventeen of 48 eyes (35.4%) with anterior Zone I disease and all 9 eyes (100%) with posterior Zone I ROP showed retinal detachment. Also, O'Keefe et al[4] reported that 17 of 24 eyes (70.8%) with Zone I ROP treated with laser showed retinal detachment. In our study, none of 18 eyes with combined intravitreal bevacizumab and Zone I sparing laser ablation showed retinal detachment. Because this study is a noncomparative study, we cannot make a direct comparison with laser monotherapy. However, we can be reasonably confident (95%) that the true rate of retinal detachment is no more than 3 in 18, or 16.7%.[25] Compared with the results of several studies mentioned above, the rate of retinal detachment in our study seems lower than that of laser monotherapy.

Several studies using combined intravitreal bevacizumab injection and laser ablation reported favorable outcomes.[12,14–16,20,26] Chung et al[14] first reported that combined laser photocoagulation and intravitreal bevacizumab (0.75 mg) injection in a patient with Zone I

plus ROP resulted in prompt regression without signs of systemic or ocular adverse events. Lee et al[15] also reported that a combination of laser photocoagulation and 0.5 mg of intravitreal bevacizumab showed a favorable outcome in 8 eyes including 1 eye with Zone I ROP. Spandau et al[12] reported that six eyes were treated with laser therapy or cryopexy and, because of the lack of regression, with bevacizumab as salvage therapy, which showed favorable outcome. In our study, combined treatment with Zone I sparing laser ablation also showed a favorable outcome. This implies that, with near-confluent laser photocoagulation on the avascular retina anterior to the Zone I and intravitreal bevacizumab, avascular retinal areas in Zone I may not necessarily be destructed by laser.

Although intravitreal bevacizumab injection may be good treatment option for Zone I ROP, its systemic effects are uncertain. Sato et al[10] reported that bevacizumab can escape from the eye into the systemic circulation and reduce the serum level of VEGF dramatically in infants with ROP. The serum VEGF levels dropped from 1,628 pg/mL to 269 pg/mL 2 weeks after the injection of a total of 0.5 mg of bevacizumab.[10] Infants with ROP are still in the process of organogenesis, and VEGF plays a role in the development of most organs.[27] Kasahara et al[28] reported that VEGF has been associated with lung maturation. Therefore, further studies evaluating the safe dose of bevacizumab are warranted.

The present study had some limitations, including the retrospective and noncomparative nature of this study, small sample size, and limited follow-up duration. Although all eyes with Type 1 ROP in Zone I showed satisfactory results, there were no eyes with posterior Zone I disease in our case series.[3,19] Thus, our results should be interpreted with caution. The results do not imply that the combined treatment is also effective for posterior Zone I disease. Also, only 8 of 18 included eyes showed Zone I disease for 12-o' clock hours. In addition, fundus photography and fluorescein angiography were not performed, which limit the precise evaluation of extent of vascularization after combined treatment.

In conclusion, combined intravitreal bevacizumab injection and Zone I sparing laser ablation for Type 1 ROP in Zone I seem to be effective treatment options. Possible advantages of our treatment strategy include lower dose of anti-VEGF, less recurrence than conventional laser photocoagulation or intravitreal bevacizumab injection monotherapy, and preservation of central visual field.

Key words: retinopathy of prematurity, bevacizumab, laser photocoagulation.

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