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ORIGINAL PAPER

Comparison of fluorescein angiographic findings in type 1 and type 2 retinopathy of prematurity with intravitreal bevacizumab monotherapy and spontaneous regression

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Abstract

Purpose To investigate the extent of vascularization of the peripheral retina and vascular development patterns in patients with type 1 retinopathy of prematurity (ROP) treated with intravitreal injection of bevacizumab (IVB) and compare fluorescein angiography (FA) findings of them to those seen in patients with type 2 ROP who have recovered spontaneously.

Methods Between May 2014 and September 2016, patients with type 1 ROP who had a single 0.025 ml (0.625 mg) IVB were evaluated as study group. On the other hand, type 2 ROP patients with stage 2 or stage 3 ROP in zone II without plus disease on indirect ophthalmoscopy were not treated and included as a control group. The progression of ROP and vascularization of retina were evaluated by FA under sedation analgesia in all patients.

Results Sixty-two eyes of 31 premature infants were included in the study: 36 eyes/18 patients were treated for type 1 ROP and 26 eyes/13 patients were followed conservatively with the diagnoses of type 2 ROP. In the last FA examination among the study group, vascular terminal was in zone II in 8 eyes/4 patients (22.22%) and in zone III in 28 eyes/14 patients (77.78%). Vascular terminal was in zone III in all eyes of the control group (100%). We noted circumferential vessels in 12 eyes/8 patients (33.3%) and 7 eyes/5 patients (26.92%) in the study and control groups, respectively. Abnormal branching was noticed in 13 eyes/7 patients (46.42%) in the control group, whereas it was not detected in the study group. Arteriovenous shunts were noted in 1 eye of a patient in the study group and in 5 eyes/4 patients in the control group. In 6 eyes/3 patients among the study group, we performed laser photocoagulation to the avascular retina because of profound vascular leakage.

Conclusion Peripheral vascular abnormalities probably occur as a result of ROP itself because similar FA findings were detected both in type 1 and type 2 ROP patients with or without treatment, although significantly less in IVB-treated group. Retinal vascularization usually reaches the farthermost limits with time even though it slows down in eyes treated with IVB, indicating the importance of a longer follow-up.

Keywords Retinopathy of prematurity · Bevacizumab · Fluorescein angiography · Peripheral vascular abnormalities

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Introduction

Retinopathy of prematurity (ROP) is a leading cause for childhood blindness especially in developing countries. It is defined as a neovascular retinal disorder resulted from delayed or abnormal retinal vessel growth in preterm neonates (mainly < 32 weeks of gestation) [1]. Vascular endothelial growth factor (VEGF) plays an important role in the development of the pathologic neovascularization in ROP [2–5]. Production and accumulation of VEGF, which is triggered by the avascular retina, eventually leads to neovascularization and retinal detachment unless it is treated on time [6, 7]. The current standard treatment of ROP is peripheral retinal ablation in order to destruct avascular retina and reduce VEGF production, which results in regression of neovascularization [8]. Anti-VEGF agents (bevacizumab, ranibizumab, and pegaptanib), which are in use of neovascular disorders, have recently been applied to infants requiring treatment for ROP, either as first-line therapy or in combination with laser treatment [9]. Intravitreal administration of a humanized monoclonal antibody against VEGF-A, namely bevacizumab (Avastin; Genentech, South San Francisco, CA), has been widely used in the treatment of ROP [10–16].

Peripheral retina is permanently destroyed with the standard diode laser therapy to treat ROP. On the other hand, intravitreal bevacizumab (IVB) allows maturation of retinal vessels after the treatment of ROP. However, it is not clear whether vascular outgrowth in type 1 ROP is affected by anti-VEGF or simply occurs as a part of disease process. In the present study, we aimed to make a more definitive conclusion by comparing fluorescein angiography (FA) findings both in patients with type 1 ROP who received IVB and in those with type 2 ROP who followed conservatively to expect a spontaneous regression.

Methods

This is a retrospective descriptive study performed in Bakirkoy Dr. Sadi Konuk training and research hospital between May 2014 and September 2016. An informed consent was obtained from all parents with regard to the off-label use of IVB (its unknown safety and efficacy for this indication) and a routine FA follow-up in the study group. Parents of control group were also informed about the advantages of FA for evaluation of the peripheral fundus, which is actually a routine procedure in our clinic. Gestational age, birth weight, postmenstrual age (PMA) which is the gestational age (GA) added with week of the postpartum age at the time of fluorescein angiography, follow-up time, and the interval between the injection times were recorded. Study group was consisted of 36 eyes of 18 patients who had undergone a single dose of IVB injection for type 1 ROP in zone I or posterior zone II. The patients who received multiple doses of IVB injections for recurrence were excluded. On contrary, all type 2 ROP patients who had stage 2 or stage 3 ROP in zone II without plus in any of the eyes or both eyes in the indirect ophthalmoscopy were included as a control group (26 eyes of 13 patients).

In the study group, IVB injections were performed by two different surgeons (AV and DYE). After the adjustment of eye speculum and instillation of 5% povidone iodine and topical anesthesia, IVB was injected at a concentration of 0.625 mg/0.025 ml (50% of the normal adult dose) using a 30-G 4-mm microneedle. All treatments were bilaterally performed on the same day. The injection was performed 1.5 mm posterior to the limbus measured by a caliper in an operating room under the care of a pediatric anesthesiologist. After the injection, the patients received topical moxifloxacin (Vigamox), 5 times/-day, for 5 days. The patients were reexamined on the next day and then were monitored weekly for the regression of the disease. Follow-up was carried out with indirect ophthalmoscopy.

Fluorescein angiography was performed with the RetCam III Imaging System (Clarity Medical Systems, Pleasanton, CA, USA). Fluorescein angiography was undertaken following administration of an intravenous bolus of 0.05 ml/kg of 10% fluorescein followed by a 3.0-ml isotonic saline flush. All images of latest FA taken were analyzed by two expert ophthalmologists (UO and ZS), and vascular abnormalities such as circumferential vessels, abnormal branching, closely packed multiple bridging arteriovenous shunts, and retinal leakage were noted. We repeated FA examination for the infants with incomplete vascularization with a 10-week interval and evaluated the images in the latest FA where the retinal vasculature reached the farthest limit. The vascular outgrowth was measured using a method that

determines the ratio of the distance from the center of the disk to the border of the vascularized zone (DB) and distance from the center of the disk to the center of the fovea (DF) [17]. With full vascularization out to the ora serrata, the ratio is 4 for the nasal and 5 for the temporal parts. The ratio of DB/DF more than 4 temporally and more than 3 nasally denotes that vascularization has reached zone III.

Results

There is no statistically significant difference between the two groups in terms of birth weight and gestational age, whereas follow-up time and age at FA examination were significantly different (Table 1). Fluorescein angiography was performed at PMAs between 54 and 97 weeks in the study group and between 43 and 86 weeks in the control group. The PMAs at the time of FA among these groups were significantly different ($p < 0.001$). The reason for this was that the follow-up of the FA images concluded early in the control group (27.31 vs. 49.33 weeks), because they reached full vascularization in a shorter time. On the other hand, follow-up was prolonged up to late period when there is no change in vascular ratio in the last two FA imaging.

Baseline diagnoses (Table 2) were as follows: In the study group, ROP stage 2+ or 3+ in posterior zone II was diagnosed in 12 infants, ROP stage 2+ or 3+ in zone I in 6 cases total 18 infants. In the control group, all 13 infants were diagnosed as ROP stage 2 or 3 in zone II without plus. As far as we know, intravitreal injection with 30-G 4-mm microneedle has been used first to treat study group. No complication during and after the injection procedure in the study group was recorded, including development of cataract. In the study group, 7 infants had recurrence of the disease after IVB injection at different PMAs between 39 and 50 weeks. No additional intravitreal injection was done to treat recurrence.

Table 3 summarizes the vascular abnormalities seen in both groups. There were one or more of the vascular abnormalities such as (1) circumferential vessels appeared morphologically similar and like a continuation of major vascular arcades with radial branches toward periphery; (2) abnormal branching or fine arborization, in the form of bundle of hair brush-like super-numerous fine vessels with bulb-like ends at the vascular and avascular junction; (3) closely packed multiple bridging arteriovenous shunts with multiple rows of vessels arching between the ends of major vessels; (4) retinal vascular leakage. Circumferential vessels were noted in 12/36 (33.3%) eyes of patients in study group and in 7/26 (26.92%) eyes in the control group, totally 19 out of 62 (30.64%) eyes. In the study group, we noted circumferential vessels in 12 eyes of 8 patients, abnormal branching in none of the eyes, closely packed multiple bridging arteriovenous shunts in 1 eye of a patient, and vascular leakage (Fig. 1) as a sign of neovascularization in 6 eyes of 3 patients. In the control group, we noted circumferential vessels in 7 eyes of 5 patients (Fig. 2), abnormal branching (Fig. 3) in 13 eyes of 7 patients, and multiple bridging arteriovenous shunts (Fig. 4) in 5 eyes of 4 patients, yet vascular leakage was detected in none of the eyes. We performed peripheral diode laser ablation to the avascular retina of those patients with vascular leakage in FA. Peripheral vascular changes were significantly higher in the control group.

In the study group, DB/DF ratio was less than 4 in temporal and 3 in nasal retina in 8 eyes of 4 (22.22%) infants so vascular terminal was found to be in zone II on the FA examination at a mean PMA of

Table 1 Some demographic data of patients

	Study group	Control group	*p* value
Gestational age (GA)	28.7 ± 3.0 (week)	28.6 ± 2.8 (week)	0.920[m]
Birth weight	1321 ± 483 (g)	1295 ± 653 (g)	0.521[m]
Time (tx to FA)	45.4 ± 11.3 (week)	–	–
PMA at treatment	36.6 ± 2.6 (week)	–	–

tx treatment, *FA* fluorescein angiography, *PMA* postmenstrual age

[m]Mann–Whitney U test

Table 2 Stages of ROP in study and control groups

Stages of ROP	Study group		Control group		*p* value
	n	%	*n*	%	
Zone I stage II plus −/+	8	22	0	0	$0.02^{\chi 2}$
Zone I stage III plus −/+	4	11	0	0	
Zone II stage II plus −/+	4	11	4	15	
Zone II stage III plus −/+	20	56	22	85	

ROP retinopathy of prematurity, *n* number of eyes, % percentage
$^{\chi 2}$Chi-square test

Table 3 Presence and types of vascular changes detected by fluorescein angiography

Vascular changes	Study group		Control group	
	n	%	*n*	%
Not detected*	17	47	3	12
Detected*	19	53	23	88
Types of changes				
Circumferential vessels	11	31	6	23
Abnormal branching	0	0	11	42
Arteriovenous (AV) shunt	1	3	3	12
Leakage	6	17	0	0
Circumferential vessels and AV shunt	1	3	1	4
Abnormal branching and AV shunt	0	0	1	4
Abnormal branching and leakage	0	0	1	4

n number of eyes; % percentage
*$p < 0.0001$ according to Chi-square test

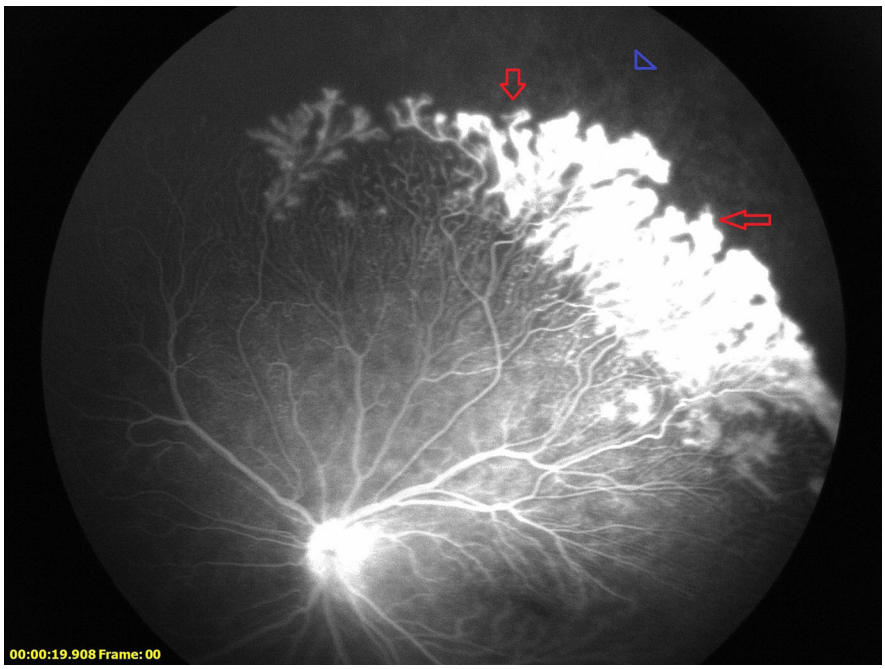

Fig. 1 Vascular leakage at the superior and temporal retina with peripheral avascularity 51 weeks after treatment of a patient with type 1 ROP. The infant was treated by IVB with the diagnosis of stage 2 ROP in zone I with plus disease at 40 weeks of PMA. Avascular retina was ablated by laser photocoagulation as a compensatory treatment

82.2 ± 12.4 week. For 28 eyes of 14 infants (77.78%), DB/DF ratio was higher than 3 in nasal (mean = 3.8 ± 0.3) and 4 in temporal retina (mean 4.4 ± 0.6) and so considered in zone III. In the control group, DB/DF ratio was higher than 3 in nasal (mean = 3.9 ± 0.1) and 4 in temporal retina (mean =

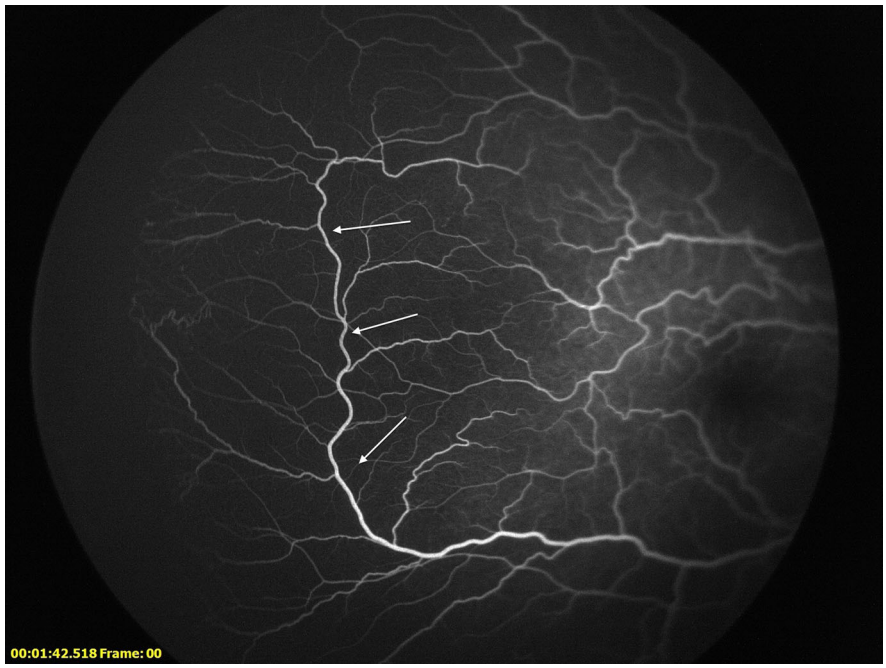

Fig. 2 Circumferential vessel with radial branches (arrow) detected in the temporal peripheral retina on FA image 47 weeks after treatment in a patient with type 1 ROP and GA of 29 weeks. The infant is treated by IVB with the diagnosis of stage 2 ROP in zone I with plus disease at 36 weeks of PMA

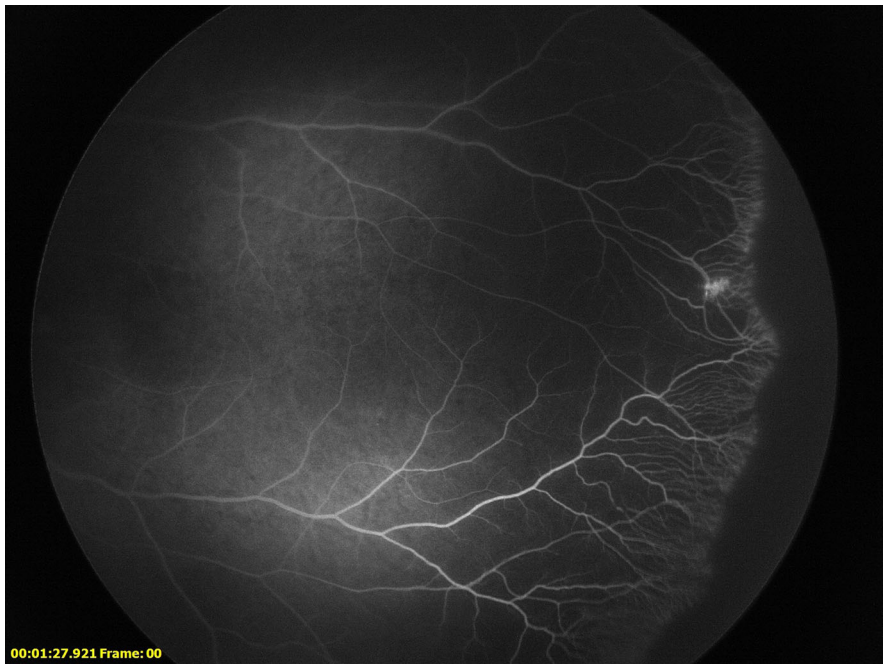

Fig. 3 Abnormal branching detected at the temporal peripheral retina of type 2 ROP patient with a GA of 29 weeks. FA image at PMA of 56 weeks

4.9 ± 0.1) in all eyes (100%). There was a statistically significant difference between two groups in terms of temporal ratio ($p < 0.001$), whereas there was no statistically significant difference for nasal ratio ($p = 0.445$).

Discussion

There are many reports about experiences of IVB in type 1 ROP [11, 18–22]. A rapid advancement of retinal vascularization from the original ROP site was usually recognized before 65 weeks of PMA after a

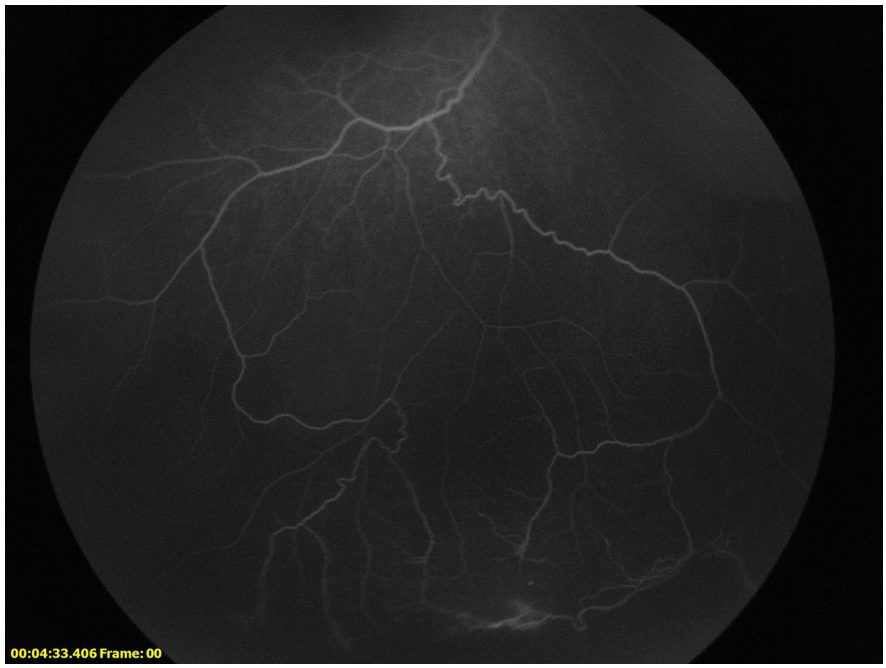

Fig. 4 Closely packed arteriovenous shunts in a patient with Type 2 ROP at 52 weeks of PMA. The patient has a GA of 25 weeks and diagnosed as stage 3 ROP in zone II without plus disease

successful IVB treatment [22]. Unlike these studies, we observed that the retinal vascularization reached the fullest extent at a longer time after IVB injection, which has been demonstrated by prolonged FA follow-up in our study patients. Final vascular outgrowth was also considered to be in zone III in 28 eyes of 14 infants (77.78%) according to FA examination at a mean PMA of 82.2 ± 12.4 weeks in the type 1 ROP group. Full vascular maturation might not be possible in type 1 ROP and achieving zone III could be considered a sufficient level for success because astrocytes would not effectively trigger vascular outgrowth into the far periphery, which could be affected due to hypoxia in the course of the disease [23]. Our findings support importance of a longer FA follow-up and reassessment of adequate level of vascular terminal after IVB in type 1 ROP before implementing an additional therapy such as laser photocoagulation [24]. We have also observed the extra benefit of intravitreal injection with 30-G 4-mm microneedle with no cataract formation.

In our opinion, the retinal periphery cannot be evaluated clearly by RetCam. For this reason, we decided to use the method developed by Lorenz et al. [17] in order to measure vascular outgrowth. Vascularization reaching zone III after IVB (87.5% of eyes in 9–187 weeks of follow-up) is suggested as an adequate response. In another study, vascular outgrowth into the periphery is an important feature and the presence of a peripheral avascular zone of less than two disk diameters may be considered normal in healthy infants [25]. In our study, vascular outgrowth of all eyes in the control group and 77.77% of eyes in the study group could reach zone III. In 8 eyes of 4 patients, vascularization was in zone II with fluorescein leakage in 6 of them, which means delayed recurrence. This indicates a high risk of development of retinal detachment following treatment with IVB [22, 23, 26]. Fluorescein leakage has been previously reported as a sign to indicate progression to severe ROP [27]. In a recent study, peripheral avascular area was also measured by unit of disk diameter and it is found to be inadequate vascularization in 42 out of 49 eyes which were treated with complementary laser photocoagulation [24]. We have only performed additional diode laser photocoagulation to avascular retina in those with retinal leakage and considered close follow-up with periodical FA examination for those without leakage after IVB injection. Our finding indicates that prophylactic laser therapy for avascular area which is supported in previous studies [12, 24] could be unnecessary in most of the patients.

On the other hand, vascular anomalies were detected in 53% of eyes in patients with IVB treatment

(study group). It is much less than that of control group (88% of eyes). The reason might be a possible positive effect of IVB to reduce vascular anomalies. However, vascular abnormalities were similar in another study [28] both in treated and untreated eyes in a sample of patients who received IVB treatment for one eye and no treatment for the other eye. It is concluded that vascular abnormalities were due to ROP itself instead of IVB treatment. Another reason of increased ratio of vascular anomalies in control group (88% vs. 53%) could be earlier FA evaluation in this group. Actually, FA was performed early in control group because vascular outgrowth reached ora serrata faster. We think that a late FA in study group in accordance with slower vascular outgrowth to reach zone III could also reduce the vascular abnormalities as a result of having much more time for vascular remodeling. Unfortunately, it is noted in another study that peripheral vascular abnormalities that were detected 9 months after injection or laser treatments had still persisted 4 years later in most of the eyes [29]. As a result, a late FA in the study group could not have a significant role to reduce the ratio of vascular abnormalities in IVB-treated infants. As a result, further studies are needed to analyze a possible positive effect of IVB to modify the course of the vascular outgrowth in ROP.

Most common vascular anomaly in study group was circumferential vessels (33.3% vs. 23% in study and control groups, respectively). Our findings are slightly less than those findings defined in normal infants/children (33.3% vs. $>$ 50%) in a previous study [25], which might also indicate a possible positive effect of IVB. On the other hand, abnormal branching at vascular avascular junction was the most common vascular alteration in the control group (46.42% vs. 0%). It contains multiple branches of thin vessels, which are newly developing and sometimes can cause minor leakage on FA at multiple points. We noted minor leakage in only one eye of an infant in the control group that ceased on 10 weeks later FA. It is not clear whether those vascular alterations have functional importance that strongly needs longitudinal studies that highlights this topic.

In conclusion, peripheral vascular abnormalities probably occur as a result of ROP itself. Although they are detected both in type 1 and type 2 ROP patients on FA imaging, vascular abnormalities are significantly less in patients who were treated with IVB which indicates that IVB might partially modify the course of retinal vascularization. Retinal vascularization slows down in eyes with anti-VEGF monotherapy, but it can reach the farthermost limits in time without the need for an additional laser therapy for avascular retina, indicating importance of prolonged FA follow-up to prevent an unnecessary laser therapy. An additional laser therapy could only be reserved for vascular leakage, which can easily be detected by FA imaging after İVB treatment in infants with type 1 ROP. Therefore, side effects of laser therapy could be avoided both by confirming expected late vascular outgrowth and by reserving laser only for vascular leakage on FA imaging. On the other hand, follow-up with FA imaging might not be routine in type 2 ROP patients because it could not probably contribute to final treatment in such patients.

Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Dr. Sadi Konuk Bakirkoy EAH ethical committee) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. It is a retrospective study; therefore, formal consent is not required.

Informed consent Informed consent was obtained from all individual participants' parents in the study, as it is routinely done before all invasive procedure.

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