• Clinical Research •

Foveal structure changes in infants treated with anti-VEGF therapy or laser therapy guided by optical coherence tomography angiography for retinopathy of prematurity

Xun Deng[1], *Yong Cheng*[1], *Xue-Mei Zhu*[1], *Dan-Dan Linghu*[1], *Hua Xu*[2], *Jian-Hong Liang*[1]

[1]Peking University People's Hospital, Eye Diseases and Optometry Institute, Beijing Key Laboratory of Diagnosis and Therapy of Retinal and Choroid Diseases, Department of Ophthalmology & Clinical Centre of Optometry, College of Optometry, Peking University Health Science Center, Beijing 100044, China

[2]Department of Ophthalmology, Children's Hospital of Soochow University, Suzhou 215003, Jiangsu Province, China

Co-first authors: Xun Deng and Yong Cheng

Correspondence to: Jian-Hong Liang. Department of Ophthalmology & Clinical Centre of Optometry, Peking University People's Hospital, 11 Xizhimen South Street, Xicheng District, Beijing 100044, China. drliangjianhong@126.com

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Abstract

● **AIM:** To evaluate foveal vessel density (VD) and foveal thickness using optical coherence tomography angiography (OCTA) in retinopathy of prematurity (ROP) children treated with laser photocoagulation or anti-vascular endothelial growth factor (VEGF) injection. Additionally, we assessed the relationship between foveal microvascular anomalies and different therapies in ROP children.

● **METHODS:** This was a single-center, retrospective study of patients with a diagnosis of type 1 ROP. Twenty-three eyes (14 patients) treated with anti-VEGF injection and twenty-nine eyes (17 patients) treated with laser coagulation were included in this study. The foveal VD, inner thickness and full thickness were measured at the central 0°, 2° to 8°, and 8° of the retina (centered on the fovea) using OCTA and cross-sectional OCT, respectively.

● **RESULTS:** Foveal VD, inner thickness and full thickness were significantly smaller within the central 8° of the retina in ROP children treated with anti-VEGF injection than in those treated with laser photocoagulation (*P*=0.013, 0.009, 0.036, respectively). The full thickness was also smaller in the anti-VEGF group than in the laser group at the central 0° of the retina (*P*=0.010). The grade of foveal hypoplasia is lower in the anti-VEGF group than in the laser group (*P*=0.045). Multivariable analysis did not find any risk factors associated with visual acuity in our study.

CONCLUSION: In children with type 1 ROP, the better structural development of fovea in those who were treated with anti-VEGF injection compared with laser photocoagulation are identified. However, visual acuity outcomes are similar 70mo after the treatments.

● **KEYWORDS:** retinopathy of prematurity; optical coherence tomography angiography; anti-vascular endothelial growth factor; laser photocoagulation

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INTRODUCTION

In infants, retinopathy of prematurity (ROP) is a common disease and the leading cause of childhood blindness[1]. Although the reported incidence of ROP varies widely, a higher proportion of preterm infants are affected by ROP in low-income and middle-income countries than in high-income countries[1-2]. ROP has been reported to occur in 26%-29.2% of very low-birth-weight (VLBW) infants in China and Singapore[3-4]. Due to the development of reproductive technologies and preterm care facilities, the preterm birth rate is increasing along with the survival rate[5]. Thus, prevention, screening, treatment, and long-term monitoring are crucial for better visual outcomes to guarantee patient quality of life.

Recently, a few studies have revealed that the foveal avascular zone (FAZ) is significantly smaller and that foveal microvascular anomalies can be observed in patients with ROP guided by optical coherence tomography angiography (OCTA)[6-7]. Chen *et al*[8] identified obvious foveal microvascular anomalies as well as higher foveal vessel density (VD) and foveal thickness in subjects measured by OCTA and optical coherence tomography

(OCT). The studies mentioned above all affirm that OCTA is a useful noninvasive technology for the visualization of the microvascular structure of the fovea.

Laser photocoagulation is still recommended as the "gold standard" treatment for ROP[6], while anti-vascular endothelial growth factor (VEGF) therapy has gradually become an innovative therapy in this disease[9]. However, the potential systemic effects and long-term ocular effects of these treatments are not fully understood[10-12]. In school-aged children, laser-treated eyes had a smaller FAZ, higher foveal VD and thicker inner retinal thickness than was found in eyes treated with anti-VEGF[13]. Most previous studies have focused on the effect of laser photocoagulation therapy on foveal structural changes. The role of anti-VEGF therapy on the foveal structure has not been fully evaluated.

Thus, the purpose of our study was to evaluate foveal VD and thickness using OCTA in ROP children treated with laser photocoagulation and anti-VEGF injection. Additionally, we assessed the relationship between foveal microvascular anomalies and different therapies in ROP children.

SUBJECTS AND METHODS

Ethical Approval This was a single-center, retrospective study of patients with a diagnosis of type 1 ROP who had received an OCTA examination in the Department of Ophthalmology, Peking University People's Hospital from January 1, 2019, to December 31, 2019. Research followed the principles of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board/Ethics Committee of Peking University People's Hospital. The trial registration number was 2017PHB179-01. Informed consents were obtained from all subjects and the participants didn't receive a stipend.

Patients The inclusion criteria were as follows: 1) Patients with a diagnosis of ROP; 2) Patients treated with laser or anti-VEGF injection once without further supplementation; 3) Patients who received OCTA examination after laser therapy or anti-VEGF injection during the study period. The exclusion criteria were as follows: 1) Patients who received supplemental laser therapy or anti-VEGF injection; 2) Patients who received therapies other than laser therapy or anti-VEGF injection during the follow-up period; 3) Patients with high refractive errors (myopia of more than 6 diopters), cataracts, glaucoma, uveitis, other retinal diseases or ocular trauma; 4) Patients who could not cooperate during the OCTA exam, resulting in poor image quality. The stage, zone, circumferential extent and presence or absence of plus disease, the indications for treatment and the treatment protocol were determined by two experienced retinal specialists according to the International Classification of Retinopathy of Prematurity[14]. All the eyes were type 1 [the early treatment for retinopathy of prematurity (ETROP)] which met the indication for early treatment according to the ETROP study[15]. Generally, eyes with Zone I or posterior Zone II lesion were treated with anti-VEGF injection, while eyes with anterior Zone II lesion or anterior fibrovascular ridge were treated with laser therapy.

The anti-VEGF agents used were either conbercept (Chengdu Kanghong Biotechnologies Co. Ltd., China) or ranibizumab (Lucentis; Novartis, Basel, Switzerland). The doses of both regimens were 0.25 mg (0.025 mL) for one intravitreal injection placed 1.5 mm posterior to the limbus. Patients in the laser group were treated with a diode laser (810 nm, Iris OcuLight Tx, Clinico Co. Ltd., Shanghai, China) photocoagulation.

All recruited patients underwent a complete followed-up ophthalmologic evaluation during the study period, including best-corrected visual acuity (BCVA) using Snellen charts, intraocular pressure, dilated indirect fundus biomicroscopy, OCTA and cross-sectional OCT.

Optical Coherence Tomography Angiography OCTA images were scanned in both eyes of all patients recruited into the study using an RT XR Avanti system (Optovue Inc., Fremont, CA, USA) with Angiovue software. This instrument uses an 840-nm superluminescent diode at an A-scan rate of 70 000 scans per second. In this study, the scanning area was 3×3 mm^2 and consisted of 304×304 A-scans centered on the fovea. Real-time eye tracking was used to corrected eye drift and reduce motion artifacts. Foveal VD was measured at the central 0°, 2° to 8°, and 8°, of the retina (centered on the fovea). Foveal VD (%) was defined as the percentage of the area of interest that was occupied by the autosegmented superficial capillary plexus and was calculated automatically by the software. The inner thickness and the full thickness were also automatically measured by the instrument software.

Structural Optical Coherence Tomography OCT was performed with the same instrument. The inner thickness and full thickness were measured at the central 0°, 2° to 8°, and 8° of the retina (centered on the fovea). The inner thickness was defined as the distance from the inner limiting membrane (ILM) to the inner plexiform layer (IPL). The full thickness of the inner boundary was segmented at the ILM with the outer boundary set as the retinal pigment epithelium (RPE). The grades of foveal hypoplasia were assessed using OCT line scan through the foveal center. The grading criteria was: normal (grade 0); absence of extrusion of plexiform layers (grade 1); grade 1 plus absence of foveal depression (grade 2); grade 2 plus absence of outer segment lengthening (grade 3); grade 3 plus absence of outer nuclear layer widening (grade 4)[16-17].

Statistical Analysis All statistical analyses were two-sided. *P* values less than 0.05 were considered statistically significant. Statistical analyses were conducted with SPSS 25.0 software (IBM SPSS, Chicago, IL, USA). The logMAR equivalents was used to represent the BCVA for further analysis.

Comparisons of baseline numeric variables (such as age, gestational age and birth weight) between groups were performed with independent sample *t*-tests or Wilcoxon rank sum tests. Comparisons of categorical variables (such as sex) between groups were analyzed with the Chi-square test.

Student's *t*-test was used to detect differences in foveal VD, inner thickness and full thickness between the anti-VEGF group and the laser group. Meanwhile, the difference in the grade of foveal hypoplasia between two groups was analysed with the Chi-square test. The means of BCVA and refraction were compared by Mann-Whitney *U* tests.

The associations between BCVA (logMAR) and potential risk factors, including gestational age, birth weight, foveal VD, inner thickness, and full thickness, were calculated with univariate linear regression and multivariate linear regression.

RESULTS

Totally 52 eyes of 29 consecutive patients receiving either laser photocoagulation or anti-VEGF injection were included during the study period. Totally 23 patients were diagnosed with bilateral ROP, while 6 patients were diagnosed with unilateral ROP. Twenty-three eyes of 14 patients (8 boys, 6 girls; mean age 5.39±0.24y) were included in the anti-VEGF group. In addition, 29 eyes of 17 patients (9 boys, 8 girls; mean age 6.78±0.47y) were included in the laser group. There was no significant difference between the two groups with regard for gestational age (30.1±1.9 *vs* 30.4±2.3wk, *P*=0.749) and birth weight (1417.7±387.1 *vs* 1445.2±414.6 g, *P*=0.865). Totally 48 eyes in the study developed ROP stage 3 in Zone II with plus disease. One eye was classified as ROP stage 3 in Zone I with plus disease and 1 eye as ROP stage 4 in Zone I with plus disease in the anti-VEGF group. There was 1 eye with stage 2 in Zone II with plus disease of ROP in the anti-VEGF group, as well as in the laser group. The mean time interval between the therapy and the OCTA examination was 70.1±18.4mo. The detailed baseline characteristics of the patients in both groups are shown in Table 1.

Table 1 Baseline characteristic of patients

Parameters	Total	Anti-VEGF group	Laser group	*P*
Patients (*n*)	29	14	17	
Eyes (*n*)	52	23	29	
Sex (M/F)	17/12	8/6	9/8	0.815
Age (y)	6.16±0.30	5.39±0.24	6.78±0.47	0.095
GA (wk)	30.2±2.1	30.1±1.9	30.4±2.3	0.749
BW (g)	1490.8±506.0	1417.7±387.1	1445.2±414.6	0.865
Stage				0.515
2	2	1	1	
3	49	21	28	
4	1	1[a]	0	
Zone				0.191
I	2	2	0	
II	50	21	29	
Plus/no plus	52	23/0	29/0	-
Follow (mo)	70.1±18.4	63.6±12.1	75.8±20.5	0.125

GA: Gestational age; BW: birth weight. [a]The patient was ROP stage 4a (without the involvement of macula) in Zone I with plus disease.

Table 2 Comparisons of optical coherence tomography angiography findings between the anti-VEGF group and the laser group

Parameters	The anti-VEGF group (*n*=23)	The laser group (*n*=29)	*P*
Foveal VD (%)			
0°	26.9±5.9	30.3±9.8	0.141
2°-8°	47.7±4.7	49.8±4.4	0.097
8°	46.2±3.7	48.8±3.5	0.013
Inner thickness (ILM-IPL, μm)			
0°	59.0±6.9	58.9±12.1	0.979
2°-8°	103.0±8.8	102.4±16.1	0.884
8°	93.0±9.2	99.6±8.5	0.009
Full thickness (ILM-RPE, μm)			
0°	258.4±13.1	272.2±23.6	0.010
2°-8°	313.8±15.0	314.3±13.9	0.887
8°	276.5±14.0	284.4±12.4	0.036

Foveal VD: foveal vessel density; ILM: Inner limiting membrane; IPL: Inner plexiform layer; RPE: Retinal pigment epithelium.

The foveal VD, inner thickness (ILM-IPL) and full thickness (ILM-RPE) were measured at the central 0°, 2° to 8°, and 8° of the retina (centered on the fovea) using OCTA. The results of the OCTA findings between the two groups are shown in Table 2. The foveal VD within the central region analyzed at 0° and 2° to 8° was similar between the two groups (*P*=0.141, 0.097). However, the foveal VD at the central 8° of the eyes was significantly smaller in the anti-VEGF group (46.2%±3.7%) than in the laser group (48.8%±3.5%; *P*=0.013). The inner thickness (ILM-IPL) within the central region analyzed at 0° and from 2° to 8° was not significantly different between the two groups (*P*=0.979, 0.884). The inner thickness at the central 8° was 93.0±9.2 μm in the anti-VEGF group and 99.6±8.5 μm in the laser group, and this difference was significant (*P*=0.009). The full thickness at the central 0° and 8° was 258.4±13.1 μm and 276.5±14.0 μm respectively, in the anti-VEGF group, and these values were significantly lower than those found in the laser group (272.2±23.6 μm and 284.4±12.4 μm, respectively; *P*=0.010 and 0.036, respectively). The full thickness within the central 2° to 8° was almost the same between the two groups (*P*=0.887). Representative OCTA images and OCT images of both groups are shown in Figures 1 and 2.

The grade of foveal hypoplasia is lower in the anti-VEGF group than in the laser group with significant difference (*P*=0.045; Table 3).

The mean spherical equivalent in both groups were -0.9±2.1 and -0.2±2.1, respectively (*P*=0.310). The mean BCVA in logMAR was similar between two groups (0.15±0.19 *vs* 0.20±0.17, *P*=0.196). The data for refraction and BCVA were shown in Table 4.

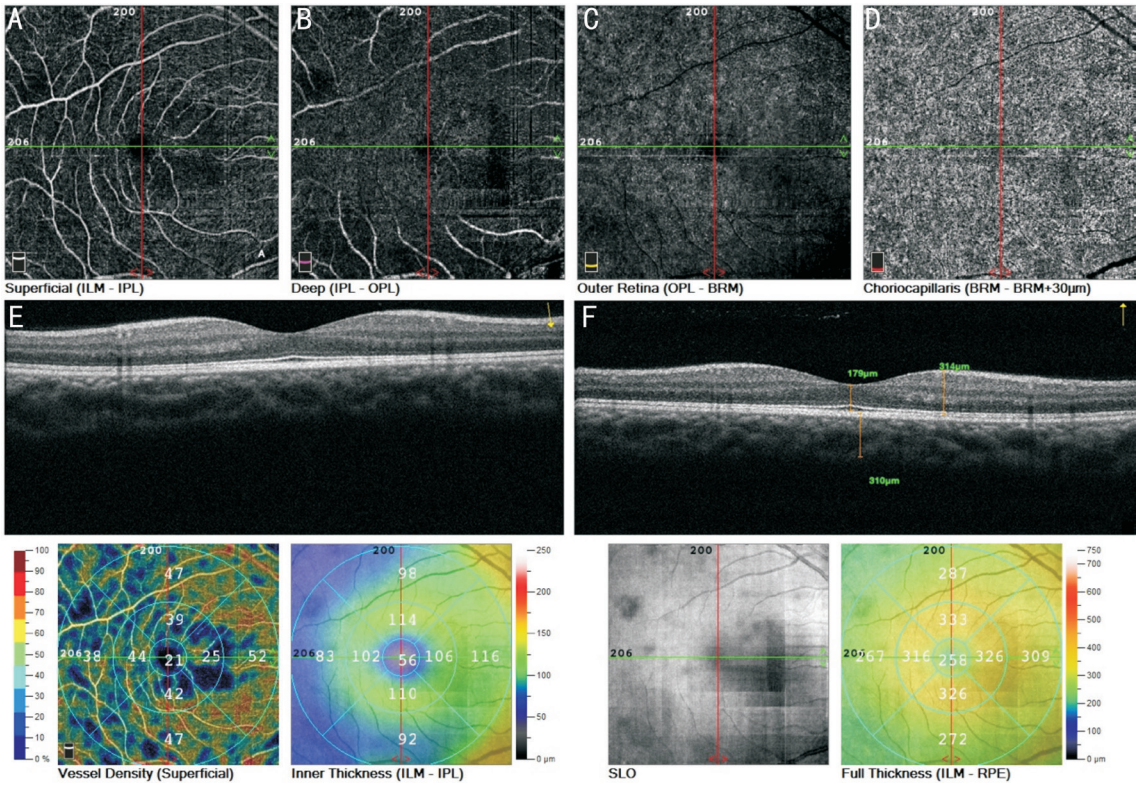

Figure 1 Optical coherence tomography angiography image of radial retinal vessels from superficial level to deep level (A-D) and cross-sectional OCT (E, F) in the anti-VEGF group The foveal VD, inner thickness (ILM-IPL) and full thickness (ILM-RPE) were automatically measured within the central 0°, 2° to 8°, and 8° of the retina (centered on the fovea).

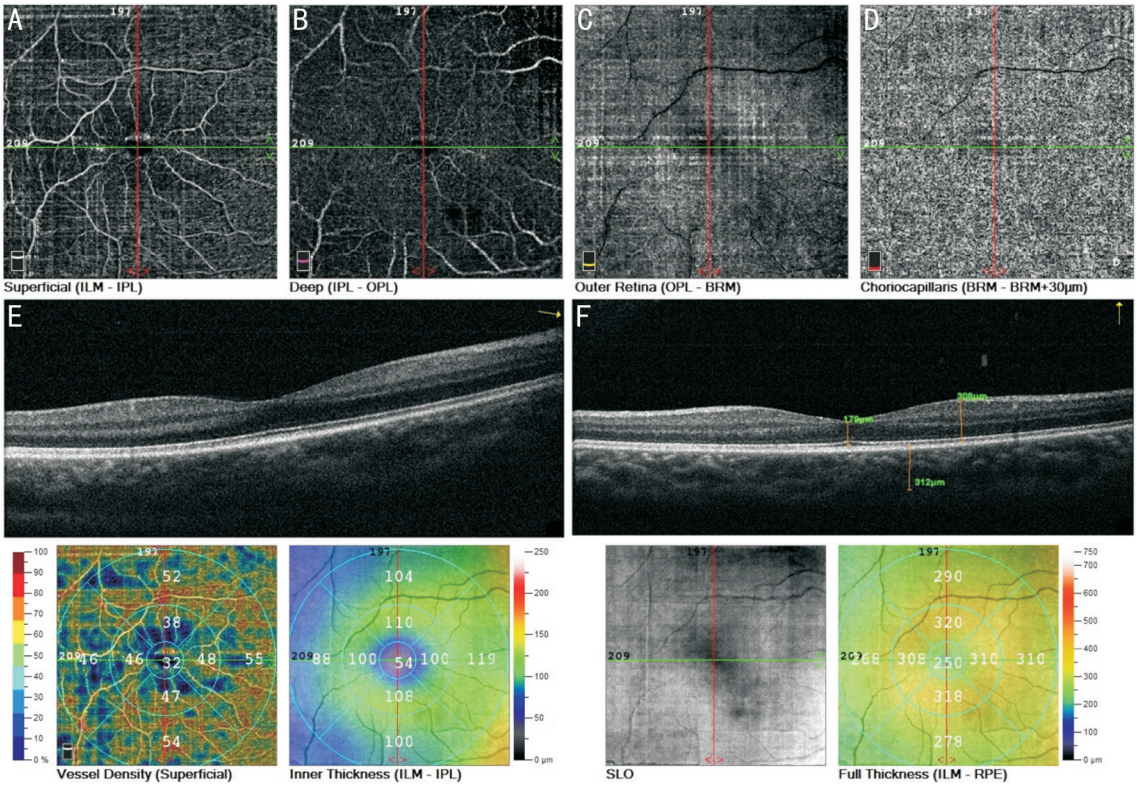

Figure 2 Optical coherence tomography angiography image of radial retinal vessels from superficial level to deep level (A-D) and cross-sectional OCT (E, F) in the laser group The foveal VD, inner thickness (ILM-IPL) and full thickness (ILM-RPE) were automatically measured within the central 0°, 2° to 8°, and 8° of the retina (centered on the fovea).

Univariate linear regression found that BCVA (logMAR) was associated with gestational age (P=0.004), birth weight (P=0.021) and foveal VD at the central 0° (P=0.035). However, after multivariate linear analysis, BCVA (logMAR)

was not statistically associated with the three factors obtained from univariate linear regression (P=0.163, 0.671, and 0.579, respectively; Table 5).

DISCUSSION

Our results show that the foveal VD, inner thickness and full thickness at the central 8° were significantly smaller in patients treated with anti-VEGF injection than in those treated with laser therapy. Moreover, the full thickness at the central 0° was higher in the laser group than in the anti-VEGF group.

OCTA is a new technological breakthrough that is ideal for evaluating structural changes in the retina and vitreous[18] and detecting vascular anomalies[18-20] in ROP. Clinically, OCTA is a noninvasive technology which can provide high-resolution images layer by layer[21] without the requirement for fluorescein dye injection. To date, only a few studies have used OCT and OCTA to investigate the FAZ and the structural changes that occur in the fovea and vessels[6-8].

During the development of foveal, retinal ganglion cells centrifugally migrated away from the center with the centripetal migration of cone cell nuclei[22]. No foveal blood vessels are present during this process[23]. The reported crucial period for the development of the fovea is 24 to 27wk of gestation[24], and its development continues in childhood, with anatomic changes until approximately 17mo postmenstrual age[25-26]. The observable markers of foveal development involves the presence or absence of retinal layers and the alternation of the thickness of retinal layers[27]. There is substantial evidence indicating that patients with immaturity show persistent inner retinal layers and well-developed outer retinal layers[28-29]. The outer retina seems to continue to develop during the postnatal period and achieve a normal structure[24]. Because of the independent development of the inner and outer layers, it has been suggested that the inner and outer layers should be measured separately[27]. Thus, we adopted both inner thickness and full thickness as parameters in our study. Rosén *et al*[30] revealed that anatomical alterations are present in the fovea in preterm children born before a gestational age of 27wk. Foveal depth was reduced and showed incomplete extrusion of the inner retinal layers, although the outer part of the fovea developed normally.

ROP is a vasoproliferative disorder mediated by VEGF[31]. Ablation of the avascular retina by laser photocoagulation is an effective therapy for ROP[32]. Recently, intravitreal anti-VEGF, applied as monotherapy or in combination with laser, has been applied in ROP children around the world[33]. However, our understanding of the effects of both treatments on the development of the fovea have not been fully described. Compared with spontaneous regression and no history of ROP, laser photocoagulation and cryotherapy have been reported to be related to a higher incidence of abnormal foveal development, including a thicker fovea with retention of the inner retinal layers and an intact outer layer and poorer visual acuity[34]. Another study of 10 premature infants with type 1 ROP treated with intravitreal ranibizumab showed that the mean central foveal thickness was higher at 1wk after the injection but then decreased until 2mo after injection[35]. The central foveal thickness was significantly different between before and at 1wk and 2mo after injection. Lepore *et al*[36] conducted a randomized controlled study of infants with type 1 zone I ROP. Their results showed that more vascular and macular abnormalities were observed in the bevacizumab group than in the laser group at the 9-month follow-up after treatment. Furthermore, at 4y of age, fewer macular abnormalities were present after treatment with bevacizumab than after laser treatment[37]. Local suppression of the level of VEGF by laser therapy may have a lesser influence than anti-

Table 3 Comparisons of the grading of foveal hypoplasia between the anti-VEGF group and the laser group *n* (%)

Grade	The anti-VEGF group (*n*=23)	The laser group (*n*=29)	*P*
0	18 (78.3)	13 (44.8)	0.045
1	5 (21.7)	15 (51.7)	
2	0	1 (3.4)	

VEGF: Vascular endothelial growth factor.

Table 4 Refractive errors and BCVA between the anti-VEGF group and the laser group

Parameters	The anti-VEGF group (*n*=23)	The laser group (*n*=29)	*P*
Spherical equivalent (D)	-0.9±2.1	-0.2±2.1	0.310
BCVA (logMAR)	0.15±0.19	0.20±0.17	0.196

D: Diopters; BCVA: Best-corrected visual acuity; VEGF: Vascular endothelial growth factor.

Table 5 Univariate and multivariate regression analysis for factors correlated with BCVA

Parameters	Univariate coefficient	*P*	Multivariate coefficient	*P*
GA	-0.032	0.004	-0.024	0.163
BW	0.000	0.021	-0.000029	0.671
Foveal VD				
0°	0.006	0.035	0.002	0.579
2°-8°	0.001	0.835		
8°	0.001	0.895		
Inner thickness				
0°	0.005	0.053		
2°-8°	-0.001	0.723		
8°	-0.002	0.409		
Full thickness				
0°	0.001	0.505		
2°-8°	-0.003	0.122		
8°	-0.003	0.159		

BCVA: Best-corrected visual acuity; GA: Gestational age; BW: Birth weight; Foveal VD: Foveal vessel density.

VEGF injection on the development of the fovea because anti-VEGF injection provides complete suppression of VEGF. Another study with a large sample size (131 preterm infants) showed that intravitreal bevacizumab injection was associated with a thicker outer retinal layer at the center of foveal[27]. Meanwhile, laser photocoagulation was related to earlier extrusion of the inner retinal layers and delayed development of the ellipsoid zone at the foveal centre[27]. That author raised the possibility that anti-VEGF injection slowed the continued migration of retinal vessels and the further development of photoreceptors beyond the fibrovascular ridge in ROP[32]. We inferred the completely suppressive effect of anti-VEGF injection would result in a short-term harmful influence on the development of foveal and then the development of foveal gradually resumed. This may explain that less foveal structural anomalies were observed in our study, since the OCTA image and OCT image were obtained approximately 70mo after the injection.

A useful working field of central retina is defined as the central 10° of visual angle which projects onto nearly the central 3 mm of retina. Furthermore, the region of central 4°-6° contains the macula and the region within 1.5 mm radius of foveal centralis is positioned at 0° eccentricity[38]. We choose the central 0°, 2°-8°, and 8° as the measurement point, since the structure of retinal in this area is significantly related with visual acuity. In our study, the foveal VD within the central 0° was almost the same in the two groups. It seems that anti-VEGF injection and laser photocoagulation have similar side effects on the VD of the fovea. As we mentioned above, foveal thickness measured by OCTA is higher in ROP eyes. The majority treated with laser photocoagulation in the study exhibited poorer degree of foveal hypoplasia. We found that the inner thickness and full thickness were smaller in patients treated with anti-VEGF than in those treated with laser therapy, consistent with Chen *et al*'s[13] study. This might indicate that anti-VEGF therapy allows the inner retina to develop towards a normal structure and resulted in better development of the fovea than was achieved by laser photocoagulation.

However, better development of the foveal didn't not result in better development of visual acuity in our study. In the linear regression, we did not identify the relationship between the foveal structure and the visual acuity. Since the sample size was small, more cases are needed to explore the potential correlations.

There are still several limitations to our study. First, the sample size was too small to draw a convincing conclusion. More cases should be collected for further analysis. Second, we only compared children treated with two methods of therapies. Preterm children with spontaneous regression were not included. Therefore, we did not have baseline data on foveal VD and retinal thickness with which to infer the real effect of the two treatments on the structure of the fovea and vessels. Third, there was a bias selection according to the treatment protocol, since more patients with immature and posterior ROP received anti-VEGF treatment while more the others with more mature ROP received laser therapy. Fourth, we did not perform a sub-analysis according to the affected ROP zone and stage. Fifth, we did not detect the relationship between visual acuity and changes in foveal structure. However, the sample size was too small to draw this conclusion. Finally, potential risk factors of visual acuity were not fully investigated in our study. In children with type 1 ROP, we identified better structural development of fovea in those who were treated with anti-VEGF injection compared with laser photocoagulation. However, visual acuity outcomes were similar 70mo after the treatments.

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