Huang *et al.*
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Effect and factors associated with reactivation after intravitreal conbercept or aflibercept in retinopathy of prematurity

Chunling Huang[1], Weikang Zou[1], Wenbei Ma[1], Jiali Li[1], Yichen Bai[1], Rong Wu[1], Qiqi Li[1], Qi Fang[1], Wenna Chen[1], Xiaohe Lu[1*] and Songfu Feng[1*]

Abstract

Background To evaluate the effect and factors associated with the reactivation of retinopathy of prematurity (ROP) after intravitreal conbercept or aflibercept.

Methods We retrospectively reviewed the medical records of 176 eyes diagnosed with ROP and treated with anti-VEGF therapy between January 2018 and September 2022. The rate of reactivation and complications were assessed during the follow-up period. The factors of reactivation of ROP after intravitreal conbercept or aflibercept were analyzed on the basis of clinical factors and retinal parameters.

Results Reactivation of ROP occurred in 10 eyes (13.9%) after intravitreal conbercept and 13 eyes (12.5%) after intravitreal aflibercept ($P=0.79$). The interval between injection and reactivation was significantly longer in the aflibercept group than in the conbercept group (15.50 ± 4.05 vs. 5.36 ± 0.50 weeks) ($P<0.001$). The central retinal arteriolar equivalent (CRAE) of aggressive ROP was larger than that of type 1 prethreshold and threshold ROP before anti-VEGF therapy ($P<0.05$). Zone I and stage 3 exhibited a positive correlation with the reactivation of retinopathy of prematurity (ROP) [odds ratio (OR) = 20.15, 5.02]. The changes in CRAE of pre-and post-therapy and gestational age were identified as potential protective factors for these outcomes (OR = 0.23, 0.49).

Conclusions Conbercept and aflibercept are effective for treating ROP. Aflibercept resulted in longer treatment intervals compared to conbercept. Zone, stage, and gestational age were associated with the reactivation of ROP. CRAE was associated with not only the severity of ROP but also its reactivation. Additionally, it may be an objective indicator in the early indication and follow-up of ROP.

Keywords Aflibercept, Anti-vascular endothelial growth factor, Conbercept, Reactivation, Retinal vessels, Retinopathy of prematurity

Background

Retinopathy of prematurity (ROP) is a developmental retinal neovascular disease of preterm infants and is particularly prevalent in developing countries [1, 2]. The incidence of ROP ranges from 10.1 to 41.5%, making it a major cause of global childhood blindness [1, 3–5]. In contrast to laser therapy, anti-vascular endothelial growth factor (anti-VEGF) therapy promotes the development of retinal vascular [6, 7]. Recently, anti-VEGF agents, including bevacizumab [8], ranibizumab [7],

*Correspondence:
Xiaohe Lu
luxh63@163.com
Songfu Feng
fsf516@163.com
[1] Department of Ophthalmology, Zhujiang Hospital, Southern Medical University, No. 253, Gongye Avenue Middle, Guangzhou 510282, Guangdong, China

conbercept [9] and aflibercept [10], have been widely used for treating ROP [6]. Compared with anti-VEGF agents of a monoclonal antibody, conbercept and aflibercept have the advantages of recombinant fusion proteins that bind VEGF-A with high affinity and longer treatment intervals [11]. As the latest anti-VEGF drugs, conbercept and aflibercept have been approved for treating retinal neovascular diseases [2, 12]. Although anti-VEGF therapy has shown considerable success, it carries risks of reactivation [9, 10].

Multiple risk factors for the reactivation of ROP have been identified in previous studies [13, 14]. The major factors of reactivation of ROP included gestational age, history of oxygen inhalation, neonatal infections, bronchopulmonary dysplasia, and necrotizing enterocolitis [13, 15]. In addition, reactivation of ROP was characterized by prominent plus disease, large vascular loops, and a rapidly progressive course [1, 13]. However, evidence to guide clinicians on the factors of reactivation of ROP after intravitreal conbercept or aflibercept is scarce. Digital imaging technology has been employed as a quantitative method for the diagnosis and prognosis of retinal diseases [16–18]. For ROP, measurement of tortuosity and dilatation has been recognized as a critical method for diagnosing plus diseases [18, 19]. Quantitative analysis can provide an objective and reproducible method for measuring retinal vascular features [18, 20].

The purpose of this study was to evaluate the efficacy of intravitreal conbercept and aflibercept for ROP. In addition, we identified factors associated with the reactivation of ROP after intravitreal conbercept or aflibercept by analyzing retinal vascular and clinical factors.

Methods

Design

We reviewed the medical records of 176 eyes diagnosed with ROP with anti-VEGF therapy at Zhujiang Hospital of Southern Medical University between January 2018 and September 2022. The study was approved by the Ethics Committee of Zhujiang Hospital of Southern Medical University and adhered to the tenets of the Declaration of Helsinki. All eyes of ROP underwent examinations by Retcam III (fundus photography). These examinations and diagnoses were performed by pediatric retinal specialists (SF and JL). The stage and zone were evaluated based on the International Classification of ROP [1]. ROP with anti-VEGF therapy was defined as type 1 prethreshold ROP, threshold ROP, and aggressive retinopathy of prematurity (A-ROP) [1, 5]. The exclusion criteria of this study were as follows: any other ophthalmic diseases except ROP (including congenital cataract, Coat's disease, glaucoma, and so on) and infants with stage 4A, 4B, 5. All parents or guardians were informed of efficacy and possible complications before anti-VEGF therapy. Informed consent was obtained in writing from the parents or guardians of each infant.

We provided detailed information to the parents of infants regarding conbercept and aflibercept separately. Intravitreal injections were performed according to the wishes and financial situation of the parents of the infants. Eyes of ROP with anti-VEGF therapy were treated with either 0.25 mg conbercept (Biotech ®) in 0.025 mL (half the adult dose) or 1.00 mg aflibercept (Eylea ®) in 0.025 mL (half the adult dose) in the operating room under sterile conditions. Infants of anti-VEGF therapy were reexamined at 24 ~ 48 h, followed by weekly to biweekly assessments until vascularization reached the peripheral serrate edge. Follow-up continued until retinal vessels developed to the periphery. The efficacy of anti-VEGF therapy was evaluated during follow-up by improvements in retinal vessel tortuosity, dilation, and regression of additional lesions, including the ridge and neovascularization. The reactivation of ROP was defined as the recurrence of retinal abnormalities after therapy, characterized by vascular dilation, tortuosity, or acute-phase plus disease. Reactivation refers to the recurrence of acute phase features, which may include new lesions and vascular changes or the need for additional treatment. Documentation of reactivation should specify the presence and location(s) of new ROP features, identified by zone and stage using the modifier reactivated [1]. Reactivation was treated with a second intravitreal anti-VEGF injection or laser therapy.

Image analysis

After the vessel segmentation mask generated by the deep learning model, the artery/vein vessel classification was performed manually by two experienced retinal specialists (SF and JL). All the images were processed and analyzed by Image J (http://rsb.info.nih.gov/ij/) and Angio Tool (https://ccrod.cancer.gov/confluence/display/ROB2/Home). This software calculated vessel density, branching index, lacunarity, central retinal arteriolar equivalent (CRAE), and central retinal venular equivalent (CRVE) among the entire segments (Fig. 1) [21, 22]. The computer automatically traced each selected vessel and calculated vessel caliber and geometric class. The changes in vessel caliber and vessel geometric class were compared pre-treatment and after 1 month of anti-VEGF therapy because the action time of anti-VEGF agents was about 1 month [23]. CRAE and CRVE were measured as average diameters of arteries and veins coursing through an area of 1/2 disc diameter surrounding the optic disc [21]. CRAE and CRVE represent retinal vascular caliber, with increased values indicating retinal vascular damage. Vessel density indicated the percentage of area occupied

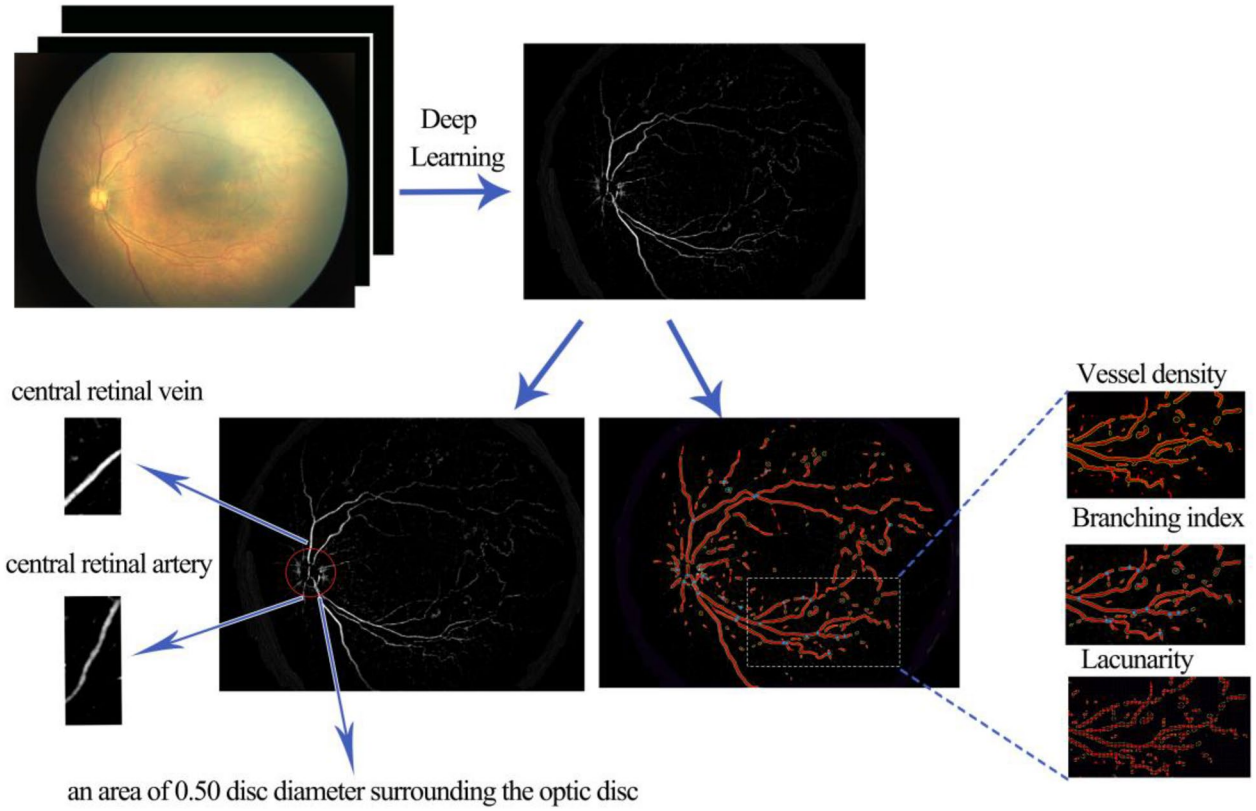

Fig. 1 Process of analysis in retinal vessels. The pictures were the representative retina and the result of analysis. Vessel outlines were shown in *red* and branching points in *blue*

by vessels inside the explant area. The branching index was defined as the number of vessel junctions. Lacunarity was defined as the mean lacunarity of all size boxes and reflected the inhomogeneity of vessels.

Statistical analysis

Medical records of infants diagnosed with ROP with anti-VEGF therapy were reviewed for sex, zone, stage, birth weight (BW), gestational age (GA), postmenstrual age, intracranial hemorrhage, history of asphyxia, necrotizing enterocolitis, history of pneumonia, patent foramen ovale, vessel caliber class, and vessel geometric class. Statistical analysis was performed with available software (SPSS, version 25.0 for Windows, SPSS, Inc.). Continuous variables were presented as means ± standard deviation. The Wilcoxon rank-sum test and Student's *t* test were used to compare the continuous variables. Categorical variables were presented as frequency (%), and the groups were compared by Chi-square and Fisher's exact tests. CRAE and CRVE in different forms of ROP were analyzed by one-way analysis of variance (ANOVA) post hoc test. To verify the factors that contributed significantly to the reactivation of ROP after anti-VEGF therapy, the related factors were analyzed by binary logistic regression analysis. The odds ratio (OR) and its 95% confidence interval (CI) for each possible factor were also calculated. The level of statistical significance was set at $P < 0.05$.

Results

Demographic characteristics

We examined the medical records of infants with ROP over 4 years and 176 eyes met the inclusion criteria. The demographics of infants are presented in Table 1.

To investigate baseline and clinical outcomes of anti-VEGF therapy for ROP, this study showed that there was no statistically significant difference in GA, BW, postmenstrual age, and sex ratio in the therapy of different anti-VEGF agents (Table 1). Reactivation of ROP occurred in 10 (13.9%) eyes after intravitreal conbercept (IVC) and 13 (12.5%) eyes after intravitreal aflibercept (IVA) ($\chi^2 = 0.07$, $P = 0.79$) (Table 1). The interval between injection and reactivation was (5.36 ± 0.50) weeks (range 4.00 ~ 6.71 weeks) in the conbercept and (15.50 ± 4.05) weeks (range 5.00 ~ 26.00 weeks) in the aflibercept. The interval between injection and reactivation was

Table 1 Demographics and clinical characteristics of infants with retinopathy of prematurity

	IVC	IVA	*P*
Sum of eyes	72	104	
Male/female	46/26	66/38	0.95
Birth weight (g)	1280 ± 340	1240 ± 410	0.52
Gestational age (weeks)	29.13 ± 2.22	29.65 ± 3.01	0.19
Postmenstrual age (weeks)	36.29 ± 1.97	36.33 ± 2.72	0.93
Rate of reactivation	13.9%(10/72)	12.5%(13/104)	0.79
The interval between injection and reactivation (weeks)	5.36 ± 0.50	15.50 ± 4.05	<0.001

IVC intravitreal conbercept, *IVA* intravitreal aflibercept

significantly longer in the aflibercept than in the conbercept ($\chi^2 = 0.93$, $P < 0.001$). CRAE of A-ROP was larger than that of type 1 prethreshold and threshold ROP before anti-VEGF therapy ($P < 0.05$, one-way ANOVA post hoc test). There was no significant difference in CRAE between type 1 prethreshold and threshold ROP before anti-VEGF therapy ($P = 0.64$, one-way ANOVA post hoc test). In addition, CRVE did not show significant differences in different forms of ROP before anti-VEGF therapy ($P > 0.05$, one-way ANOVA) (Fig. 2).

Factors associated with reactivation

To identify the factors of reactivation of ROP, associations of explanatory variables with reactivation were examined by binary logistic regression analysis. Relevant variables included zone, stage, GA, BW, postmenstrual age, intracranial hemorrhage, history of asphyxia, necrotizing enterocolitis, history of pneumonia, patent foramen ovale, vessel caliber class, and vessel geometric class. The study showed that GA was associated with the reactivation of ROP (OR = 0.49; 95% CI 0.29 ~ 0.81; $P = 0.01$) (Table 2). In terms of retinal characteristics, zone I (OR = 20.15; 95% CI 1.62 ~ 250.30; $P = 0.02$) and stage 3 (OR = 5.02; 95% CI 1.23 ~ 20.47; $P = 0.03$) were associated with reactivation of ROP. Additionally, changes in CRAE of pre- and post-therapy were associated with reactivation of ROP (OR = 0.23; 95% CI 0.06 ~ 0.91; $P = 0.04$). However, the changes of CRVE, vessel density, branching index, lacunarity, BW, postmenstrual age, intracranial hemorrhage, history of asphyxia, necrotizing enterocolitis, history of pneumonia and patent foramen ovale were not associated with reactivation of ROP ($P > 0.05$) (Table 2).

Discussion

This study identified that conbercept and aflibercept are effective treatments for ROP. Compared with conbercept, aflibercept resulted in longer treatment intervals. Zone, stage, changes in CRAE of pre- and post-therapy, and gestational age were significantly associated with reactivation of ROP after intravitreal conbercept or aflibercept. We demonstrated that CRAE exhibited fewer variations in the infants with reactivation of ROP after anti-VEGF therapy. In addition, the CRAE in cases of A-ROP was larger than that of type 1 prethreshold and threshold

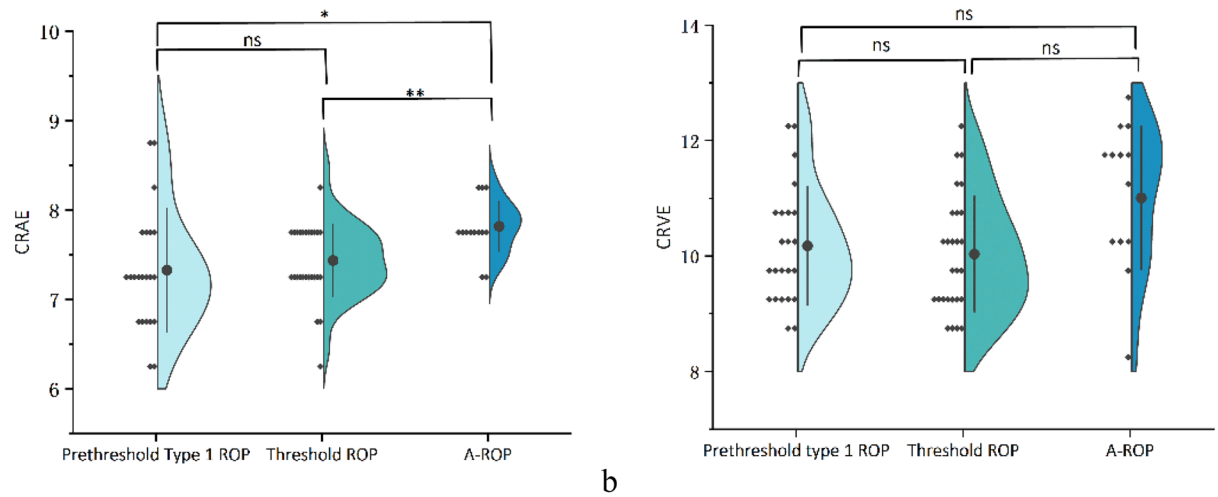

Fig. 2 Violinplot showed the differences between CRAE and CRVE in different forms of ROP before anti-VEGF therapy. **a** CRAE in different forms of ROP is compared by software. CRAE of A-ROP was larger than that of type 1 prethreshold ROP ($P = 0.029$). CRAE of A-ROP was larger than that of threshold ROP ($P = 0.009$). There was no significant difference in CRAE between type 1 prethreshold and threshold ROP ($P = 0.637$). **b** CRVE in different forms of ROP is compared by software. CRVE did not show a significant difference in different forms of ROP ($P > 0.05$). nsp > 0.05, *$P < 0.05$, **$P < 0.01$, one-way analysis of variance post hoc test. *ROP* retinopathy of prematurity, *anti-VEGF* anti-vascular endothelial growth factor, *CRAE* central retinal arteriolar equivalent, *CRVE* central retinal venular equivalent

Table 2 Logistic regression models showing variable associated with reactivation of retinopathy of prematurity

Variable	OR	95% CI	*P* value	Nagelkerke R square
Gestational age (weeks)	0.49	0.29 ~ 0.81	**0.01**	
Postmenstrual age (weeks)	1.16	0.94 ~ 1.43	0.16	
Birth weight (g)	13.48	0.87 ~ 209.90	0.06	
Intracranial hemorrhage (yes)	1.33	0.47 ~ 3.80	0.60	
History of asphyxia (yes)	2.38	0.88 ~ 6.48	0.09	
Necrotizing enterocolitis (yes)	2.25	0.53 ~ 9.64	0.27	
History of pneumonia (yes)	0.63	0.18 ~ 2.14	0.46	
Patent foramen ovale (yes)	1.31	0.48 ~ 3.62	0.60	
Zone I	20.15	1.62 ~ 250.30	**0.02**	
Stage 3	5.02	1.23 ~ 20.47	**0.03**	
Changes of posterior retinal vessels before and after treatment				
CRVE	2.05	0.96 ~ 4.37	0.06	
CRAE	0.23	0.06 ~ 0.91	**0.04**	
Vessel density	0.67	0.37 ~ 1.21	0.19	
Branching index	0.02	0.0004 ~ 1.26	0.07	
Lacunarity	121.37	0.02 ~ 631,842.43	0.27	
				0.60

CI confidence interval, *OR* odd ratio, *CRAE* central retinal arteriolar equivalent, *CRVE* central retinal venular equivalent

ROP, indicating that CRAE may be closely associated with the severity and reactivation of ROP.

Anti-VEGF agents have become effective treatments for ROP [7, 10, 24]. Of all anti-VEGF agents, conbercept and aflibercept offer advantages as recombinant fusion proteins with high VEGF-binding affinity and longer treatment intervals [10, 24]. In our study, the interval between injection and reactivation was longer in the aflibercept than in the conbercept. Aflibercept is a recombinant fusion protein (molecular weight, 115 kDa) and composed of the extracellular ligand-binding sequences of VEGFR1 (domain 2) and VEGFR2 (domain 3) attached to the Fc portion of human immunoglobulin IgG [10, 23]. Whereas conbercept is a recombinant fusion protein (molecular weight, 143 kDa) that contains the second extracellular domain of VEGFR1, the third and fourth extracellular domains of VEGFR2, and the Fc region of human IgG [9]. The binding affinity of aflibercept to VEGF-A165 is almost 100-fold greater than those of ranibizumab and bevacizumab, whereas the affinity of conbercept to VEGF is 50-fold higher than that of bevacizumab [23, 25]. Due to its distinct pharmacokinetic profile, aflibercept may have a longer half-life and slower clearance from systemic circulation than conbercept, potentially contributing to the extended treatment interval. Conbercept and aflibercept are effective for treating ROP. However, these agents displayed different activities in the infant's eye during the follow-up period. Clinicians and the parents of the infants should pay attention to the interval and frequency of follow-up. The interval for fundus screening after intravitreal conbercept is shorter than that of aflibercept. Close monitoring of the fundus should be conducted in infants approximately 1 month after initiating conbercept treatment, with particular attention to any signs of reactivation.

The analysis of factors associated with the reactivation of ROP after intravitreal conbercept or aflibercept is limited. Reactivation of ROP is often underdiagnosed because of loss of follow-up. Therefore, individualized examinations and treatment of ROP should be carefully devised by considering the factors of reactivation. Recent studies have identified that several factors are associated with the reactivation of ROP, including GA, mechanical ventilation, supplemental oxygen, and respiratory distress syndrome [26, 27]. We found that GA is a factor associated with the reactivation of ROP, As GA increases, the probability of reactivation is relatively decreased. In contrast, we found that birth weight had little correlation with reactivation of ROP which is consistent with the findings of some studies [13, 15, 28].

Currently, only a few studies have focused on retinal features in the reactivation of ROP. In this study, we quantified retinal vascularization characteristics. Vessel caliber and vessel geometric classes were analyzed on the basis of CRAE, CRVE, vessel density, branching index, and lacunarity. This study demonstrated that the changes in CRAE of pre- and post-therapy were associated with the reactivation of ROP. As changes in CRAE of

pre- and post-therapy increases, the probability of reactivation is relatively low. Most studies have reported that retinal artery diameter is associated with retinal hypoxia [29, 30]. We speculated that CRAE is associated with retinal hypoxia. Minimal changes in the retinal arteries after anti-VEGF therapy may indicate more severe retinal hypoxia. In addition, in terms of the different forms of ROP, the CRAE of A-ROP was larger than those of type 1 prethreshold and threshold ROP before monotherapy. Severe ROP is associated with posterior retinal vessel dilation [1].

However, the changes in CRVE of pre- and post-therapy were not significantly associated with the reactivation of ROP, and CRVE did not show significant differences in the different forms of ROP. Given that retinal arteries contain more oxygen than retinal veins [29, 30], arteries may be more sensitive to hypoxic changes than veins. It is widely accepted that the oxygen demand of tissues drives retinal vessel development, with hypoxia-induced vascular growth factors mediating this process [29, 31]. In premature infants, the retinal vessels are incomplete, and retinal vascular endothelial cells with relative hypoxia are regulated by many angiogenetic factors [29]. Vascular endothelial cell injury leads to hemodynamic changes, which may affect retinal arteries. In addition, administration of anti-VEGF agents might induce not only widespread loss of the retinal capillary beds but also maldevelopment of the retinal vessels [8]. Thus, they may result in severe retinal ischemia and continuous VEGF release followed by reactivation of ROP.

The present study has limitations that must be considered, including the retrospective nature of the data set and the small sample size of infants with ROP. The limited samples, attributed to our stringent inclusion criteria, were carefully selected to minimize potential bias. In addition, the study was conducted at a single center, which may limit the generalizability of the findings. Future research with larger cohorts and extended follow-up is needed for a more comprehensive evaluation. Despite these limitations, retinal vascular features may be regarded as an objective indicator of the reactivation of ROP after anti-VEGF therapy, offering a potential new direction for monitoring and understanding ROP reactivation.

Conclusions

Both conbercept and aflibercept are effective treatments for ROP. Compared with conbercept, aflibercept resulted in longer treatment intervals. Zone stage, gestational age, and changes in CRAE of pre- and post-therapy were associated with reactivation of ROP. Notably, CRAE was associated with not only related to the severity of ROP but also the reactivation of ROP, highlighting its potential as a valuable indicator in monitoring ROP progression.

Abbreviations

A-ROP	Aggressive retinopathy of prematurity
BW	Birth weight
CRAE	Central retinal arteriolar equivalent
CRVE	Central retinal venular equivalent
GA	Gestational age
IVA	Intravitreal aflibercept
IVC	Intravitreal conbercept
OR	Odds ratio
ROP	Retinopathy of prematurity
VEGF	Vascular endothelial growth factor

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Author contributions

Songfu Feng and Xiaohe Lu participated in topic selection, designed, and analyzed materials. Chunling Huang and Weikang Zou contributed equally to the draft of this article, collected the data, and wrote this draft. Wenbei Ma, Jiali Li, Yichen Bai, and Wenna Chen did the injection and scanning work during the period of examination and follow-up. Rong Wu, Qiqi Li, and Qi Fang collected data and revised this article.

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

This study protocol was reviewed and approved by the Ethics Committee of Zhujiang Hospital of Southern Medical University. Parents of each infant wrote informed consent before treatment. This research was carried out in line with a named standard.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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