Dynamic Analysis of Ocular Fundus Changes After Different Doses of Bevacizumab in the Treatment of Retinopathy of Prematurity in Threshold Period

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Research Article

Keywords: Retinopathy of prematurity, threshold period, vitreous injection, bevacizumab, fundus examination

Posted Date: September 20th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-430209/v2

Abstract

Purpose: To analyze the efficacy of three different doses of bevacizumab treatment on Threshold retinopathy of prematurity during different periods .

Methods: 36 cases (72 eyes) of infants with threshold ROP were analyzed, whom were treated with intravitreal injection of 1.25 mg, 0.75 mg or 0.5 mg bevacizumab respectively from October 1st, 2016 to September 30th, 2017. After treatment, fundus examination results during five time points were recorded and classified into four grades according to the efficacy.

Results: There were significant differences in the changes of fundus among the 3 groups from the 4th day to the 4th week after treatment （P<0.01）. In the 1.25 mg group, there was a significant difference in the changes of fundus on the 4th day after treatment VS. the 2nd week after treatment (P<0.001). In the 0.75 mg and 0.5 mg group respectively, the changes of fundus were significantly different between each consecutive time points of the 4th day, 2nd week, 4th week and 2nd month after treatment (P<0.001,P=0.001,P=0.002; P<0.001,P=0.001,P=0.003). The proportion of normal retinal vessels respectively in 1.25 mg , 0.75 mg and 0.5 mg group is 66.67%、43.48% and 50% in the 3rd month after treatment.

Conclusion: Retinal complete vascularization was slightly better in 1.25 mg group, but failed to reach a statistical significance. Based on results, the lowest dose 0.5 mg may be preferred since our final results were similar (p>0.05). Long-term follow-up of fundus changes was still needed to avoid recurrence of ROP whatever the dose of bevacizumab was uesed.

Key Messages

- Intravitreal injection of anti-VEGF drugs(bevacizumab) is one of the main surgical methods for ROP. But at present there are no relevant reports about the comparition of efficacy, peripheral retinal complete vascularization and recurrence of different doses of injection bevacizumab on ROP .
- In three doses of bevacizumab(1.25mg, 0.75mg, 0.5mg) treatment, their efficacy (the 3th month) were similar, but the efficacy of 1.25 mg group was the best from the 4th day to the 4nd week after treatment. The fundus change of 0.5 mg and 0.75 mg group is significantly from the 4th day to the 2nd month after treatment on patients with threshold ROP. So long-term follow-up of fundus changes was still needed to avoid recurrence of ROP whatever the dose of bevacizumab was uesed.

Introduction

Retinopathy of prematurity (ROP) is characterized by the abnormal development and proliferation of immature retinal vessels, which is one of the main causes of blindness in premature infants. It is often found in preterm infants with low gestational age and low birth weight. For the infants with the risk of developing ROP, ophthalmologists should carry out routine fundus examination, early diagnosis and early

treatment [1]. At present, retinal photocoagulation and intravitreal injection of anti-VEGF drugs are the main therapies for zone I or II ROP such as APROP, pre-threshold or early threshold ROP. Comparing with the traditional laser therapy, intravitreal injection of anti-VEGF comprises the advantages of less operation time, less risk to damage visual field or develop high myopia caused by the destruction of peripheral retinal structure, less and delayed recurrence of ROP, and continued normal vascularization of peripheral retina[2–4]. The commonly used anti-VEGF drugs include bevacizumab and ranibizumab.

At present, there is no unified standard for the use of bevacizumab in the treatment of ROP worldwide. The injection dose could be 0.05 ml (1.25 mg), 0.03 ml (0.75 mg), or 0.025 ml (0.625 mg), etc, or even less, in once or multiple times of treatment [5]. Clinical studies have found that several doses of bevacizumab treatment have achieved positive results in the treatment of threshold ROP, but the peripheral retina may not continue to vascularize or ROP recurrence may occur after the treatment. Therefore, it is recommended to closely follow up the fundus changes and perform surgical treatment if necessary [6–8].

However, there are no relevant reports on the efficacy, peripheral retinal vascularization cycle and recurrence rate of ROP after different doses of bevacizumab, which makes it impossible to provide a unified standard for the optimal effective dose of bevacizumab treatment and follow-up schedule for threshold ROP. Therefore, in this study, we aimed to assess the efficacy of three different commonly used doses of intravitreal Bevacizumab injection(IVB) (1.25 mg, 0.75 mg, 0.5 mg) on patients with threshold ROP

Methods

Study cohort

This is a retrospective study enrolling 36 infants (72 eyes) with threshold ROP diagnosed in our hospital from October 1st, 2016 to September 30th, 2017, including 27 males and 9 females. The gestational age was 26-34 weeks, with an average of (29.19 ± 1.95) weeks; the birth weight was 0.75-1.96 kg, with an average of (1.23 ± 0.28) kg. They were randomly divided into three groups for both eyes IVB 0.05 ml (1.25 mg), 0.03 ml (0.75 mg), and 0.02ml (0.5 mg) respectively. Preterm infants with unstable vital signs during treatment or requiring laser would be excluded from this study.

Examination and treatment

Before treatment, the patient's pupil were dilated and examined with RetCam (Massie Laboratory, U.S.), a pediatric wide-range digital fundus imaging system. The examination results were interpreted by two different senior Pediatric Ophthalmologists. The patients whom were diagnosed with threshold ROP were divided into three groups and were treated respectively. During the treatment, ECG monitoring and the assistance of nurses and anesthesiologists were provided. The basic steps are as follows: 1. Anesthesia of conjunctiva with 0.5% procaine eye drops 5 minutes before the operation; 2. Routine local disinfection of the treated eye; 3. Opening the eyelids of the treated eye with the special pediatric eyelid opener; 4.

Gently clamp the limbus of the treated eye with ophthalmic forceps to fully expose the injection area. Drug was injected intravitreally using a 30-gauge needle placed 1-1.5 mm behind the limbus. Different dosage of bevacizumab solution (Roche Group, U.S.) was injected slowly. After the injection, the needle was slowly withdrawn, and the injection port was pressed with a cotton swab until the bleeding was stopped and no liquid outflow was observed. In the end, the conjunctival sac was coated with TobraDex eye ointment, and the treated eye was covered with a small gauze.

Follow-up

The patients were reexamined with RetCam on 4 days, 2 weeks, 4 weeks, 2 months and 3 months after treatment. The results were recorded. The main outcomes were evaluated according to the CRYO-ROP and ETROP study [9-10]. (1) According to the changes of fundus (curative efficacy), all cases could be described in four grades: Grade I, Taking effect – the reduction of retinopathy and plus disease; Grade II, Remarkable effect – the reduction of retinopathy and the disappearance of plus disease; Grade III, Curing -- the disappearance of retinopathy and plus disease; Grade IV, retinal complete vascularization – disappearance of retinopathy and plus disease, with complete vascularization of peripheral retinal. (2) Definition of recurrent ROP: The retinopathy that did not regress or got even worse, with retinal neovascularization or bleeding.

Data analysis

SPSS 23.0 statistical software was applied to analyze the data. The fundus examination results on 4 days, 2 weeks, 4 weeks, 2 months and 3 months after treatment were recorded and analyzed using K-Independent Samples test.

Results

Results showed no significant difference in gestational age, birth weight or corrected gestational age among the three groups (Table 1). In 1.25 mg group, 75% (18 / 24) cases were in grade II, 8.33% (2 / 24) cases were in grade I and 16.67% (4 / 24) cases were in grade III on the 4th day after treatment. With the extension of follow-up interval, 33.33% (8 / 24) cases ended in grade III and 66.67% (16 / 24) cases ended in grade IV on the 3rd month after treatment;In 0.75 mg group, 50% (12 / 24) cases were in grade I and 50% (12 / 24) cases were in grade II on the 4th day after treatment. On the 4th week after treatment, one of the patients was found to have recurrent retinopathy and received laser photocoagulation. On the 3rd month after treatment, 54.17% (13 / 24) cases ended in grade III and 41.67% (10 / 24) cases ended in grade IV In 0.5 mg group, 58.33% (14 / 24) cases were in grade I and 41.67% (10 / 24) cases were in grade II on the 4th day after treatment. With the extension of follow-up interval, 50% (12 / 24) cases ended in grade III and 50% (12 / 24) cases ended in grade IV on the 3rd month after treatment.

Table 1
Comparison of gestational weeks, birth weight and corrected gestational age at treatment among different doses of bevacizumab groups

	1.25mg Bevacizumab	0.75mg Bevacizumab	0.5mg Bevacizumab	P
Gestational weeks (weeks)	29.38 ± 1.89	29.09 ± 2.44	29.11 ± 1.60	0.927
Weight (kg)	1.30 ± 0.34	1.26 ± 0.25	1.13 ± 0.23	0.334
Corrected gestational age at treatment (weeks)	36.40 ± 2.52	36.33 ± 2.79	38.30 ± 1.61	0.084
*P<0.05				

Comparing among the three doses of bevacizumab treatment, there were both significant differences in the efficacy from the 4th day to the 4th week after treatment ($P < 0.001$, $P < 0.001$, $P < 0.045$). But there was no significant difference on the 2nd month and 3rd month ($P = 0.696$, $P = 0.262$) (Table 2). In 1.25 mg group, there was a statistical difference ($P < 0.001$) on the 4th day after treatment comparing with the 2nd week after treatment. However, there was no statistical difference comparing among other time points; In 0.75 mg group, there were statistical differences between two consecutive time points on the 4th day, 2nd week, 4th week and 2nd month after treatment ($P < 0.001$, $P = 0.001$, $P = 0.002$). However, there was no significant difference on the 2nd month VS. 3rd month ($P = 0.55$); In 0.5 mg group, there were statistical differences between two consecutive time points on the 4th day, 2nd week, 4th week and 2nd month after treatment ($P < 0.001$, $P = 0.001$, $P = 0.003$). However, there was no significant difference on the 2nd month VS. 3rd month ($P = 0.077$) (Table 3). **Discussion**

Table 2
Comparison of fundus changes (curative efficacy) among different doses of bevacizumab groups during different periods after treatment

	Bevacizumab dosage	Fundus changes					
		Grade I	Grade II	Grade III	Grade IV	χ^2	P
The 4th day	1.25mg	2	18	4	0	17.873	0*
	0.75mg	12	12	0	0		
	0.5mg	14	10	0	0		
The 2nd week	1.25mg	0	0	24	0	19.910	0*
	0.75mg	2	10	12	0		
	0.5mg	0	14	10	0		
The 4th week	1.25mg	0	0	22	2	6.199	0.045*
	0.75mg	0	1	22	0		
	0.5mg	0	3	21	0		
The 2nd month	1.25mg	0	0	18	6	0.725	0.696
	0.75mg	0	0	15	8		
	0.5mg	0	0	18	6		
The 3rd month	1.25mg	0	0	8	16	2.681	0.262
	0.75mg	0	0	13	10		
	0.5mg	0	0	12	12		
*P<0.05							

Table 3
Comparison of fundus changes (efficacy) among different periods after treatment in three doses of bevacizumab groups

	1.25mg		0.75mg		0.5mg	
	χ^2	P	χ^2	P	χ^2	P
The 4th day VS. The 2nd week	32.696	0*	18.148	0*	24.011	0*
The 2nd week VS. The 4th week	2.043	0.153	11.998	0.001*	10.791	0.001*
The 4th week VS. The 2nd month	2.350	0.125	10.069	0.002*	9.027	0.003*
The 2nd month VS The 3rd month	8.217	0.004*	0.357	0.55	3.133	0.077
*P<0.05						

Discussion

Nowadays, the efficacy of anti-VEGF treatment on ROP has been confirmed in many aspects. Bevacizumab and ranibizumab are the most commonly used anti-VEGF drugs in clinic. The latter may have less systemic effects than the former, because it has a shorter half-life in the blood. It was found that after intravitreal injection of ranibizumab, plasma VEGF levels decreased the next day, but returned to normal after one week [11]. In another study, it was found that the recurrence rate of ROP patients treated with the first injection of ranibizumab may be higher, because it could vanish from the ocular local more quickly [12]. A large study [13] showed that 127 eyes (45%) of 283 eyes relapsed after intravitreal injection of ranibizumab. For these reasons, we chose bevacizumab, which is also the most commonly used anti-VEGF drug for ROP in the world.

Results in our study showed that the curing rates of 1.25 mg, 0.75 mg and 0.5 mg bevacizumab treatment also were 100% in the 2^{nd} month after treatment. And the proportion of retinal complete vasculization respectively in 1.25mg , 0.75mg and 0.5mg group is 66.67%, 43.48% and 50% in the 3rd month after treatment. In comparison, Henaine-Berra A. et al. studied 47 eyes of 26 patients with threshold or pre-threshold ROP treated with 0.75 mg bevacizumab, with regular fundus fluorescein photography and Retcam examination, and found that the cure rate was 92%, with 45% of the patients did not complete normal retinal vascularization[14]. However, Wu W.C. et al. conducted a multicenter study in Taiwan, and found that the cure rate of patients with stage 3 ROP treated with once 0.625 mg bevacizumab was 90%, with 10% of the cases needed additional laser treatment [15]. The above reports are similar to the experimental results of 0.5 mg and 0.75 mg groups in our study, suggesting that regular review is still needed after bevacizumab treatment to prevent recurrence.

Considering the potential effects of anti-VEGF drugs on the organs of the whole body, experts have been trying to use low-dose bevacizumab to treat ROP. Wallace et al. [16] used intravitreal injection of 0.25 mg, 0.125 mg, 0.063 mg or 0.031 mg bevacizumab in 61 eyes with type I ROP in a single-blinded multicenter study. They found that low-dose bevacizumab treatment has positive effects, but many eyes needed

additional treatment. Dikci S. et al. Also confirmed the above results in a clinical study of 0.5 mg and 0.625 mg bevacizumab in the treatment of acute posterior pole retinopathy of prematurity (AP-ROP), in which the recurrence rate of the 0.5 mg group was higher, and half of the eyes needed further photocoagulation at the corrected gestational age of 47.6 ± 1.5 weeks [17]. In the 0.5 mg group of our study, the cure rate was 100% and the retinal complete vascularization rate was 50% on 3 months after treatment (corrected gestational age 49-50 weeks), with no recurrent cases. Considering the limited number of cases and insufficient follow-up time, further study is still needed. However, based on the current literature reports, we believe that ROP treated with lower dose bevacizumab is more likely to recur.

For the postoperative evaluation of bevacizumab-treated ROP, fundus examination should be carried out regularly. The wide-angle digital fundus photography system (RetCam) and fluorescein angiography can be used to evaluate and analyze [18-19]. Because the latter requires intravenous injection of fluorescein sodium contrast agent, there is a certain risk for the infants, so it is not recommended to be used repeatedly. Therefore, at present, we mainly use fundus photography equipment such as RetCam for examination. Our study showed that the curative efficacy of IVB was different under different doses or under different periods. On the 4^{th} day and 2^{nd} week after treatment, the curative efficacy of 1.25 mg group was better, and there was no difference among the three groups after 4 weeks. The fundus change of 0.5mg and 0.75mg group is significantly from the 4^{th} day to the 2^{nd} month after treatment. The proportion of retinal complete vasculization respectively in 1.25mg, 0.75mg and 0.5mg group is 66.67%, 43.48% and 50% in the 3^{rd} month after treatment. The results also showed that the efficacy of bevacizumab in the 1.25 mg group was better than other two groups within 4 weeks after treatment, however we believe it should not be simply deducted that the efficacy of low-dose bevacizumab is not obvious, because the efficacy was similar in three groups from postoperative 2^{th} to 3^{th} month. Long-term postoperative fundus review and dynamic observation are needed. As long as the no deterioration of retinopathy was observed after treatment, additional therapy is not necessary. Up till now, there is no related research report.

In terms of disease recurrence, multiple studies have found that comparing with photocoagulation, the average recurrence time of retinopathy treated with IVB is about 10 weeks later. Therefore, it is suggested that for the treatment of ROP with IVB, the follow-up time should be longer, so as to detect the recurrence of the disease [20-21]. The three groups of patients in this study were all nonlocal and could not adhere to the long-term follow-up, so they only followed up to the 3^{rd} month after treatment, and then followed up in the local hospital. In the 0.75 mg group, one patient was found to have a recurrence of ROP in the left eye 4 weeks after treatment, and laser treatment was given. The eye was excluded from the study from the 4^{th} week to the 3^{rd} month after treatment. No recurrence was found in other cases. Because the pharmacokinetic duration of bevacizumab in newborns may be longer than that in adults, the efficacy, recurrence rate and safety of bevacizumab may be different. At the same time, the blood-retinal barrier of ROP infants is not fully developed. Therefore, the results of bevacizumab injection in preterm infants are different from that of adults. Intraocular injection of bevacizumab in preterm infants had been proven to reduce serum VEGF level [22]. whereas, many organs of ROP infants are not fully developed. The

decrease of VEGF concentration in blood may affect the develop of nervous system, kidney, lung and other related organs. Arima M. et al. conducted a 10-year retrospective study, and used the Kyoto Scale of Psychological Development (KSPD) to evaluate the neurodevelopment of type I ROP patients treated with early use of 0.625mg bevacizumab injection at the age of 18 months. The results showed that the treatment may lead to the impairment of interpersonal relationship, social communication and / or speech ability development in premature infants[23]. Therefore, we suggest that low-dose bevacizumab should be used in the treatment of ROP.

Summary: Retinal complete vascularization was slightly better in 1.25 mg group, but failed to reach a statistical significance. Based on results, the lowest dose 0.5 mg may be preferred since our final results were similar (p>0.05). Long-term follow-up of fundus changes is still needed to avoid recurrence of ROP whatever the dose of bevacizumab is uesed for treatment of ROP . More studies with larger samples are required to find the adequate dose in ROP management.

Declarations

Funding The study was funded by The Guangzhou Medical and health science and technology project in 2016（No. 20161a010034）.

Conflicts of interest None of the authors have any proprietary interest in any material mentioned. The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors' contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Jianxun Wang, Tian Liu and Ying Yu. The first draft of the manuscript was written by Feng Chen and Daoman Xiang. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval/Consent for publication This study was approved by the ethic committee of scientific research of Guangzhou Women and Children's Medical Center before the implementation of the project. The informed consents of the parents of the enrolled infants were obtained before the treatment.

Clinical trials registration Our study was registered in China clinical trial registry（No.ChiCTR2100043345）

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Figures

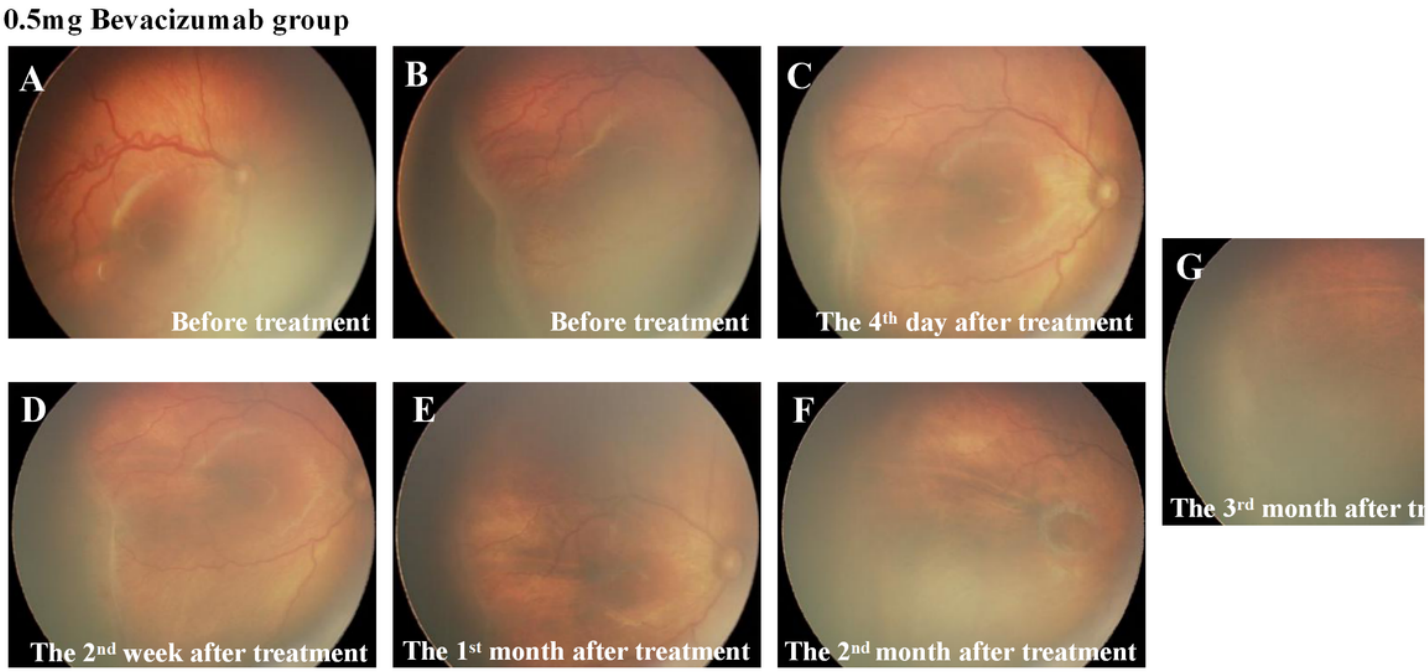

Figure 1

A preterm infant with gestational age of 26 weeks + 5 days and birth weight of 750g, with corrected gestational age of 36 weeks + 5 days, was diagnosed with bilateral zone II, stage 3 + ROP. The 0.02 ml (0.5 mg) bevacizumab was injected into the vitreous cavity of both eyes. Before treatment: (A-B)In the right eye, the thickening grayish white fibrous membrane proliferation was found in zone II of the temporal retina. A large gray avascular area was found in the peripheral retina. Central and branch vessels dilated tortuously (plus change). Fundus examination on the 4th day after treatment: (C) In the right eye, the proliferation of fiber membrane on the temporal retina was reduced comparing with that before treatment. And the plus disease was alleviated. (D) Two weeks after treatment, the temporal retinopathy of the right eye was further alleviated. However, there was still a large avascular area in the peripheral retina. (E) One month after treatment, the temporal retinopathy of the right eye showed "linear change", without plus disease. However, there was still a large avascular area in the peripheral retina. (F)Two months after treatment, the temporal retinopathy of the right eye completely disappeared, and the avascular area in the peripheral retina was shrunk, without plus disease. (G) Three months after treatment, the peripheral retina of the right eye had been vascularized without any lesions or plus disease.

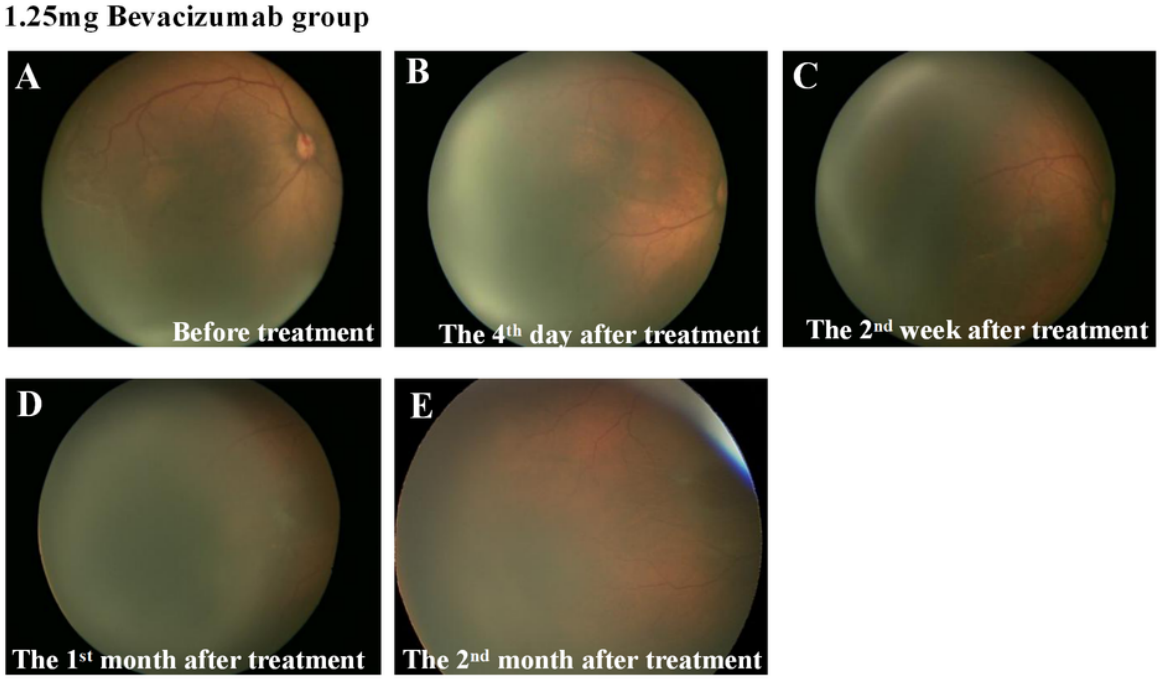

Figure 2

A preterm infant with 29 gestational weeks and birth weight of 1400g, with corrected gestational age of 41 weeks, was diagnosed with bilateral zone II stage 3 + ROP. 0.05 ml (1.25 mg) bevacizumab was injected into the vitreous cavity of both eyes. Before treatment: (A) In the right eye, the proliferation of the thickening fibrous vascular membrane was found in the zone II of the temporal retina. And a large gray avascular area was found in the peripheral retina. The central and branch vessels dilated tortuously. Fundus examination on the 4th day after treatment:(B) In the right eye, the fibroproliferative lesions on the temporal retina have disappeared. A large avascular area was found in the peripheral retina, without plus disease. (C) Two weeks after treatment, the avascular area in the peripheral retina of the right eye was shrunk, without any lesions or plus disease. (D) One month after treatment, the avascular area in the peripheral retina of the right eye was further shrunk, without any lesion or plus disease. (E) Two months after treatment, the peripheral retina of the right eye had completed vascularized, without any lesions or plus disease.

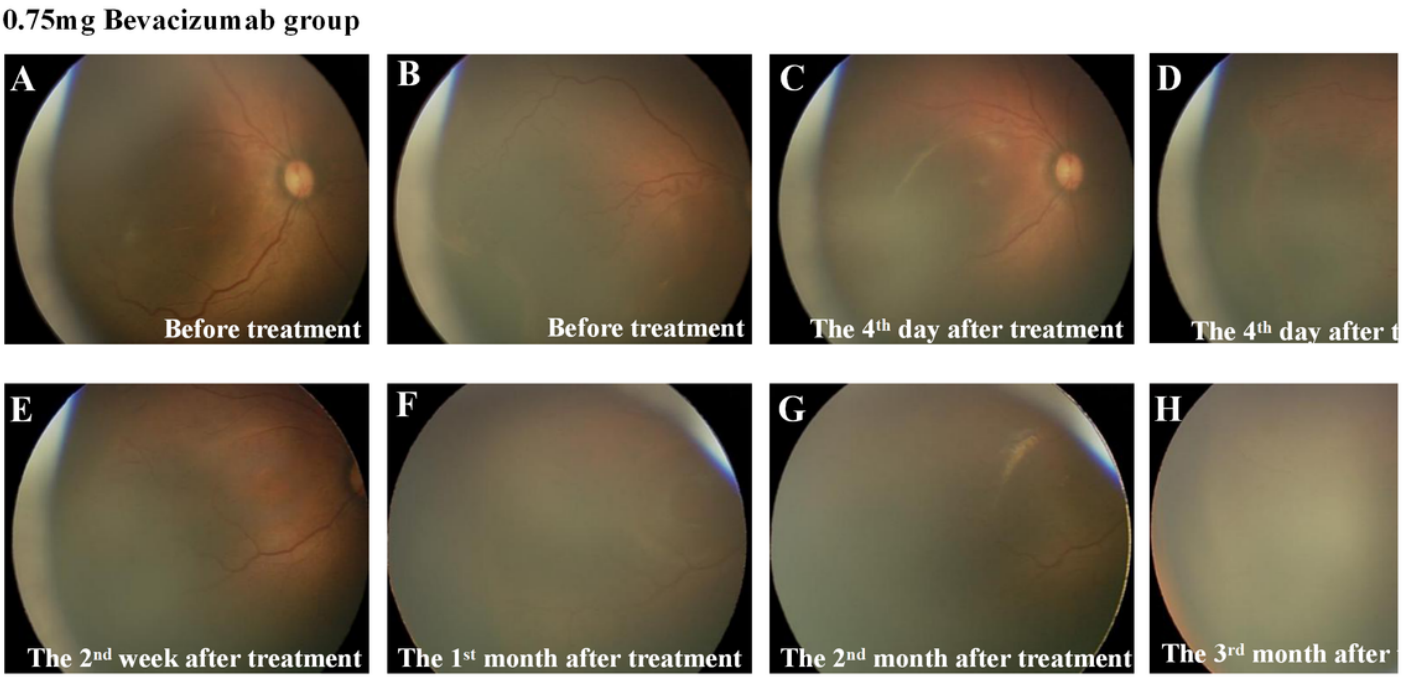

Figure 3

A preterm infant with gestational age of 27 weeks + 1 day and birth weight of 1000g, with corrected gestational age of 34 weeks + 3 days. The diagnosis before treatment: bilateral zone II stage 3 + ROP. 0.03ml (0.75mg) bevacizumab was injected into the vitreous cavity of both eyes. Before treatment: (A-B) In the right eye, the thickening fibrous vascular membrane was found in zone II of the temporal retina of the right eye. A large gray avascular area was found in the peripheral retina. The central and branch vessels dilated tortuously (plus disease). Fundus examination on the 4th days after treatment: (C-D) The proliferation of retinal fibrovascular membrane and the plus disease in the temporal retina of the right eye were alleviated comparing with those before treatment. (E) On 2 weeks after treatment, the temporal retinopathy of the right eye was further alleviated, without plus disease. However, there was still a large avascular area in the peripheral retina. One month after treatment, the temporal retinopathy of the right eye showed "linear change", without plus change. There was still a large avascular area in the peripheral retina. Two months after treatment, the temporal retinopathy of the right eye completely disappeared. And the avascular area in the peripheral retina was shrunk, without plus disease. Three months after treatment, the temporal retinopathy of the right eye completely disappeared, and the peripheral retina was basically vascularized without plus disease.