Int J Clin Exp Med 2019;12(9):11249-11256
www.ijcem.com /ISSN:1940-5901/IJCEM0092760

Original Article

The clinical efficacy of vitreous injection of ranibizumab in patients with ocular fundus disease and its effect on hemorheology

Binke Yu[1], Zhinan Liu[2]

[1]*Department of Ophthalmology, Xianyang Hospital of Yan'an University, Xianyang, Shaanxi, China;* [2]*Department of Ophthalmology, Changzhou Third People's Hospital, Changzhou, Jiangsu, China*

Received February 19, 2019; Accepted April 10, 2019; Epub September 15, 2019; Published September 30, 2019

Abstract: Objective: To explore the clinical efficacy of ranibizumab in patients with fundus disease. Methods: 78 patients with ocular fundus diseases were randomly divided into observation group (n=39) and control group (n=39). Patients in the observation group were treated with ranibizumab by intravitreal injection, while patients in the control group were treated with conbercept by intravitreal injection. Postoperative intraocular pressure, postoperative visual acuity improvement, treatment outcome, blood rheology indexes such as plasma viscosity, red blood cell aggregation index and red blood viscosity were measured and compared before treatment and after treatment (1 week). The hemodynamic parameters such as peak systolic velocity (PSV), end diastolic velocity (EDV), and resistance index (RI) before and after treatment were detected and compared by color ultrasound. Results: The intraocular pressure and visual acuity of the observation group were improved more significantly than those of the control group ($P<0.05$). The total effective rate of the observation group was significantly higher than that of the control group ($P<0.05$). The plasma viscosity, red blood cell aggregation index and red blood viscosity index of the observation group was significantly improved compared with those of the control group ($P<0.05$). After treatment, the PSV and EDV of the observation group were significantly higher than those of the control group, and the RI of the observation group was significantly lower than that of the control group ($P<0.05$). The incidence of postoperative complications in the observation group was significantly lower than that in the control group ($P<0.05$). The quality of life scores of the observation group were significantly higher than those of the control group ($P<0.05$). Conclusion: Vitreous injection of ranibizumab can effectively improve the hemodynamic indexes and life quality, which is worthy of clinical application.

Keywords: Vitreous injection, ranibizumab, ocular fundus disease, hemorheology

Introduction

As a common ophthalmic disease, ocular fundus diseases can involve multiple sites such as the retina, optic disc, and choroid. It has a relatively complicated pathogenesis and diverse forms of disease [1, 2]. Ocular fundus diseases can cause serious damage to the patient's vision, and complications will occur. If not treated in time, blindness is very likely to occur, which has a very serious impact on patients' life and physical and mental health [3]. As the fundus of the eye is located in the deep part of the eye and has a complex and delicate structure, it is difficult for conventional medicine and physical therapy to achieve good efficacy [4]. For example, laser therapy, hormone therapy, vitrectomy and other treatment methods have certain therapeutic effects, but these treatment methods may cause serious complications such as angiogenesis or macular edema in patients, which cannot be completely cured [5, 6].

Ranibizumab is a new anti-angiogenic drug that binds to vascular endothelial growth factor (VEGF) and is a second-generation humanized anti-vascular endothelial growth factor recombinant mouse monoclonal antibody fragment. Previous studies have shown that patients with ocular fundus diseases are often accompanied by abnormalities in blood rheology and vessel

wall [7, 8]. This will lead to an increase in the patient's blood viscosity, causing the blood flow to slow down, eventually forming microthrombus and causing ischemia and hypoxia in the choroid and retina [9, 10]. Therefore, while ocular fundus diseases are being treated, efforts should be made to improve the patient's hemodynamics and microcirculation and increase blood flow to the ocular fundus, which is of great clinical significance in improving the therapeutic effect of ocular fundus diseases [11].

Although there were studies on the efficacy of ranibizumab in the treatment of ocular fundus diseases, studies on the effects of ranibizumab on hemodynamics in patients with ocular fundus diseases have been relatively rare. Therefore, we explored the clinical efficacy of vitreous injection of rezumumab in patients with fundus disease and its effect on hemorheology.

Materials and methods

General information

78 patients with ocular fundus diseases were enrolled in our hospital, including 41 male patients and 37 female patients, with an average age of (40.1±4.6) years. Among them, there were 16 cases of diabetic retinopathy (DR), 19 cases of retinal vein occlusion, 21 cases of hypertensive ocular fundus diseases, and 22 cases of related macular degeneration. Patients were randomly divided into observation group and control group, with 39 cases in each group. Patients in the observation group were treated with ranibizumab by intravitreal injection, while patients in the control group were treated with conbercept by intravitreal injection.

Exclusion and inclusion criteria: Inclusion criteria: Patients were diagnosed with ocular fundus diseases by fluorescein angiography and optical tomography. Exclusion criteria: patients who underwent ocular treatment in the past month; patients with other ocular lesions such as cataract or glaucoma; patients with severe liver and kidney dysfunction; patients with malignant tumors were excluded; patients with severe cardiovascular and cerebrovascular disease; patients with cognitive impairment or communication impairment; and patients who did not cooperate with the study. All patients and their families agreed to participate in the trial and signed an informed consent form. This experiment has been approved by the hospital ethics committee.

Treatment method

All patients were given antibiotic eye drops to the eyes 2 hours before treatment, and the conjunctival sac was washed with 500 ml of sodium chloride solution containing 160,000 units of gentamicin. In the operating room, the patient was given a conventional towel, followed by a topical anesthetic with acaine. After anesthesia, at the flat portion of the ciliary body 4 mm behind the limbus of the eye, the syringe was punctured into the vitreous cavity, perpendicular to the sclera. After determining the position of the syringe needle, the control group was injected with 0.1 ml of conbercept (purchased from Chengdu Kanghong Biotechnology Co., Ltd., Chinese Drug Approval Number: S20-130012), and the observation group was injected with 0.1 ml of ranibizumab (purchased from Nocartis Pharma Stein AG, Approval number: S20110085). After the drug was slowly injected, the needle position was gently pressed with a cotton swab. At the end of the surgery, Tobradex eye ointment (0.3% tobramycin, 0.1% dexamethasone) was applied to the patient's conjunctival sac and then bandaged with a sterile dressing. The patients needed to rest in bed on the day of surgery. All patients underwent regular reexamination after surgery.

Outcome measures

(1) The postoperative intraocular pressure and postoperative visual acuity improvement were recorded and compared between the two groups. (2) After 1 week of treatment, the therapeutic effects of the two groups of patients [12] were evaluated. According to the recovery of the patient, the treatment effect included markedly effective (the degree of recovery of the patient's vision was >0.1, the visual field defect was greatly reduced, the clinical symptoms disappeared, and the intraocular pressure returned to normal), effective (patient's visual acuity was improved, intraocular pressure gradually recovered before treatment, and visual field defects decreased) and ineffective (clinical symptoms did not disappear, patients' visual acuity continued to decline, and intraocular pressure and visual field defects did not

Table 1. General data of the two groups of patients

Factor		Observation group n=39	Control group n=39	X^2/t	P
Gender	Male	21 (53.85)	20 (51.28)	0.051	0.821
	Female	18 (46.15)	19 (48.72)		
Age	≥40	22 (56.41)	23 (58.97)	0.053	0.819
	<40	17 (43.59)	16 (41.03)		
BMI (kg/m^2)	≤22	21 (53.85)	22 (56.41)	0.052	0.82
	>22	18 (46.15)	17 (43.59)		
Course of disease (year)		5.21±1.09	5.33±1.08	0.488	0.627
Cultural level	Below high school	12 (30.77)	13 (33.33)	0.059	0.808
	High school and above	27 (69.23)	26 (66.67)		
Type of disease	Diabetic retinopathy	8 (20.51)	8 (20.51)	0.100	0.992
	Retinal vein occlusion	9 (23.07)	10 (25.64)		
	Hypertensive fundus disease	11 (28.21)	10 (25.64)		
	Related macular degeneration	11 (28.21)	11 (28.21)		
	Vision	0.16±0.02	0.15±0.02		
	Intraocular pressure (mmHg)	15.2±2.1	15.3±2.3		
Coagulation function	APTT s	28.31±2.11	28.29±2.08	0.042	0.967
	PT s	11.66±1.21	11.63±1.25	0.108	0.915
	FIB g/l	3.15±0.22	3.13±0.21	0.411	0.683
Renal function index (μmol/L)	Creatinine	57.89±5.17	58.21±4.94	0.28	0.781
	Urea	5.33±0.61	5.41±0.68	0.547	0.586
	Uric acid	261.55±12.79	264.31±13.01	0.945	0.348

improve). Total effective treatment = (markedly effective number + effective number)/total number × 100%. (3) Blood rheology indexes such as plasma viscosity, red blood cell aggregation index and red blood viscosity were measured and compared before treatment and 1 week after treatment. (4) The hemodynamic parameters such as peak systolic velocity (PSV), end diastolic velocity (EDV), and resistance index (RI) before and after treatment were detected and compared by color ultrasound. (5) The complications of the two groups were recorded and compared. Complications included increased intraocular pressure, intraocular infection, retinal hemorrhage, and hard exudation. (6) The QOL-LC quality of life scale [13] was used to evaluate the quality of life of patients. The scale includes five aspects: physical function, role function, emotional function, cognitive function and social function. The lower the score, the worse the quality of life.

Statistical methods

In this experiment, the statistical software SPSS 20.0 (Beijing Wangshu Times Technology Co., Ltd.) was used to analyze and process the experimental data. The count data is expressed in percentage and number of cases. Chi-square test was used for comparison between groups. The comparison between the groups of measurement data was performed by independent t test, and the comparison before and after treatment in the group was performed by paired t test. $P<0.05$ indicates that the difference was statistically significant.

Results

General data comparison

There were no significant differences in gender, age, BMI, and disease type between the two groups, which were comparable (**Table 1**).

Comparison of postoperative intraocular pressure and postoperative visual acuity in both groups

The intraocular pressure and visual acuity of the two groups were improved compared with those before treatment, but the intraocular pressure of the observation group was signifi-

Table 2. Postoperative intraocular pressure and postoperative visual acuity improvement in both groups

Factor	Observation group n=39	Control group n=39	t	P
Postoperative intraocular pressure	12.47±0.39	14.09±0.22	22.59	<0.001
Postoperative visual acuity	0.57±0.17	0.29±0.16	7.490	<0.001

Table 3. Curative effect in the two groups of patients after treatment [n, (%)]

Curative effect	Observation group n=39	Control group n=39	X^2	P
Markedly effective	24 (61.54)	20 (51.28)	0.834	0.361
Effective	13 (33.33)	9 (23.08)	1.013	0.314
Invalid	2 (5.13)	10 (25.64)	6.303	<0.050
Total effective rate	37 (94.87)	29 (74.36)	6.303	<0.050

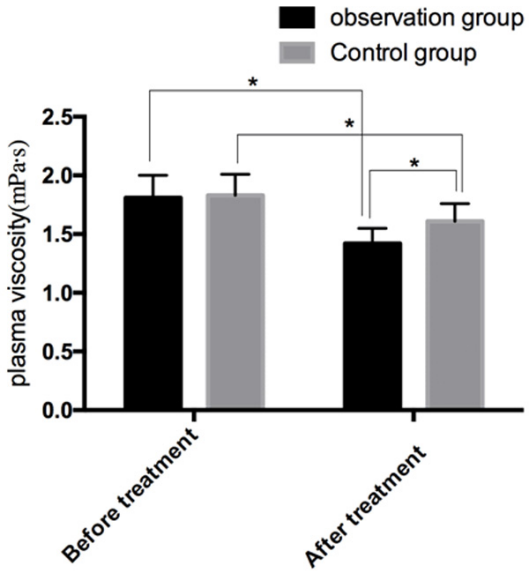

Figure 1. Comparison of plasma viscosity between the two groups of patients before treatment and 1 week after treatment. The plasma viscosity of the two groups was improved compared with that before treatment. However, the plasma viscosity of the observation group was significantly improved compared with that of the control group, and the difference was statistically significant (P<0.05). Note: *indicated P<0.05.

cantly improved compared with that of the control group (P<0.05). See **Table 2** for details (**Table 2**).

Comparison of therapeutic effects between the two groups of patients

In the observation group the total effective rate was 90%. In the control group the total effective rate was 63.33%. The total effective rate of treatment in the observation group was significantly higher than that in the control group (P<0.05) (**Table 3**).

Comparison of plasma viscosity, red blood cell aggregation index and red blood viscosity index between two groups of patients before treatment and 1 week after treatment

The plasma viscosity, red blood cell aggregation index and red blood viscosity index of the two groups 1 week after treatment were significantly higher than those before treatment (all P<0.05, **Figures 1**-**3**). However, compared with those of the control group, the plasma viscosity, red blood cell aggregation index and red blood viscosity index of the observation group were significantly improved (all P<0.05, **Figures 1**-**3**), which indicated that ranibizumab by intravitreal injection can improve the plasma viscosity, red blood cell aggregation index and red blood viscosity.

Changes in PSV, EDV and RI before and 1 week after treatment

There was no significant difference in PSV, EDV and RI between the two groups before treatment (all P>0.05, **Figures 4**-**6**). The PSV, EDV and RI of the two groups were significantly improved 1 week after treatment than those before treatment (all P<0.05, **Figures 4**-**6**). However, PSV and EDV of the observation group were significantly higher than those of the control group after treatment (P<0.05, **Figures 4** and **5**), and RI was significantly lower than that in the control group (P<0.05, **Figure 6**). These data indicated that the ranibizumab for intravitreal injection significantly improved the PSV and EDV, but inhibited the RI.

Postoperative complications in both groups

The percentage of patients with intraocular pressure, intraocular infection, retinal hemorrhage, and rigid exudation of complications incidence in the observation group was 5.13%. The number of patients with intraocular pres-

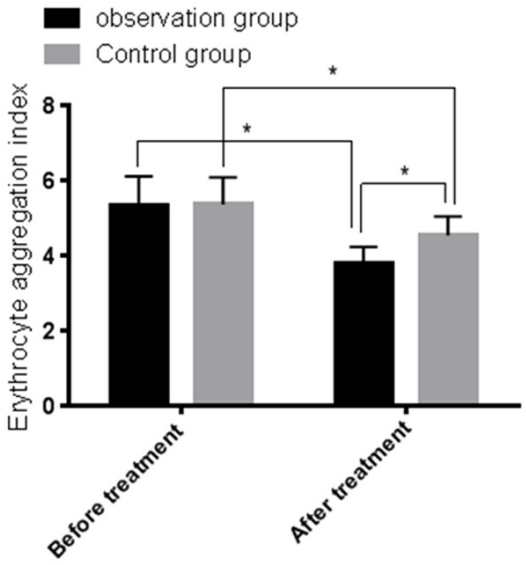

Figure 2. Comparison of red blood cell aggregation index between the two groups of patients before treatment and 1 week after treatment. The red blood cell aggregation index of the two groups after treatment was improved compared with that before treatment. However, the red blood cell aggregation index of the observation group was significantly improved compared with that of the control group, and the difference was statistically significant (P<0.05). Note: *indicated P<0.05.

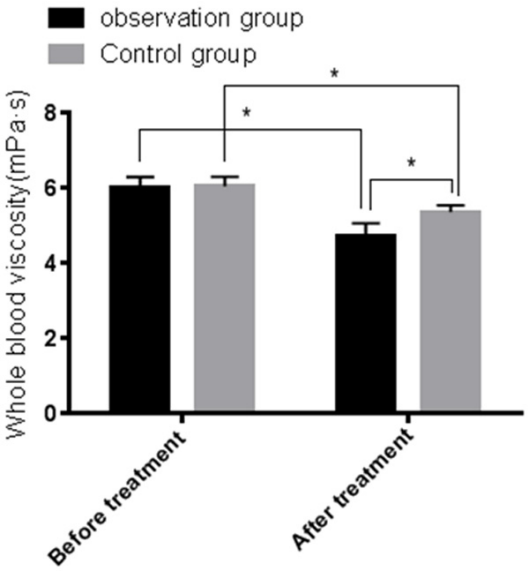

Figure 3. Comparison of red blood cell viscosity in the two groups of patients before treatment and 1 week after treatment. The red blood cell viscosity of the two groups was improved compared with that before treatment. However, the red blood cell viscosity of the observation group was significantly improved compared with that of the control group, and the difference was statistically significant (P<0.05). Note: *indicated P<0.05.

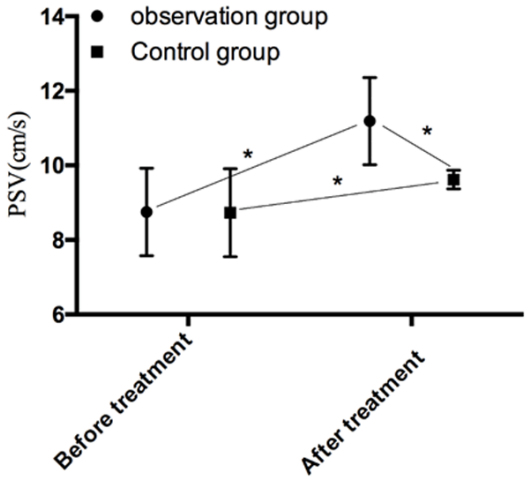

Figure 4. PSV changes in both groups before and 1 week after treatment. The PSV of the two groups improved compared with that before treatment. However, the PSV of the observation group was significantly improved compared with that of the control group, and the difference was statistically significant (P<0.05). Note: *indicated P<0.05.

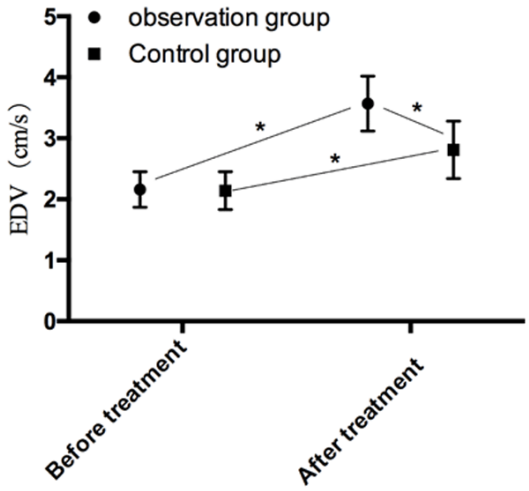

Figure 5. EDV changes in both groups before and 1 week after treatment. The EDV after treatment in both groups was improved compared with that before treatment. However, the EDV of the observation group was significantly higher than that of the control group after treatment, and the difference was statistically significant (P<0.05). Note: *indicated P<0.05.

sure, intraocular infection, retinal hemorrhage, and rigid exudation in the control group was 3, 2, 4, and 2, respectively. The percentage of patients with intraocular pressure, intraocular infection, retinal hemorrhage, and rigid exudation of complications incidence in the control group was 28.21%. The incidence of postoper-

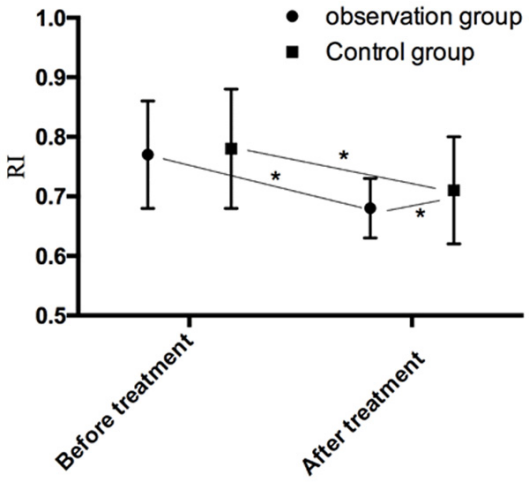

Figure 6. RI changes in both groups before and 1 week after treatment. The RI of the two groups was improved after treatment, but the RI of the observation group was significantly lower than that of the control group after treatment (P<0.05). Note: *indicated P<0.05.

ative complications was significantly lower in the observation group than in the control group (P<0.05) (**Table 4**).

Comparison of quality of life between the two groups of patients at 1 month after surgery

The quality of life scores of the patients in the observation group were significantly higher than those in the control group. (P<0.05) (**Table 5**).

Discussion

Ocular fundus diseases have a wide variety of categories and complex causes. As long as there is a lesion in the papilla, choroid or retina of the optic nerve, it may cause a defect in the vision field, which will affect vision, and even lead to blindness in severe cases [14]. Many patients with ocular fundus diseases are associated with varying degrees of vascular wall structure changes and hemodynamic abnormalities. This usually leads to the increase of blood viscosity in patients, which further leads to the blockage of capillaries, resulting in the insufficient blood supply and hypoxia of local tissues in the fundus of the eye, such as retina and choroid, and aggravating the vascular remodeling [15, 16]. Therefore, increasing the blood supply to the fundus and improving the patient's microcirculation and hemodynamics are important directions for the treatment of ocular fundus diseases. Ranibizumab can inhibit the formation of new blood vessels by binding to VEGF, which promotes the rapid absorption of retinal fluids and reduces blood rheology such as red blood viscosity and plasma viscosity. At the same time, it can help improve the microcirculation of the fundus of the patient, increase the blood supply to the eye, and promote the recovery of vision of the patient [17, 18]. VEGF is a substance that can promote the dissolution of extracellular matrix, lumen formation and cell proliferation and migration, thus promoting the formation of retinal angiogenesis [19]. Conbercept is also a drug that specifically binds to VEGF for the purpose of treating fundus diseases [20]. Therefore, conbercept was used as a control to explore the clinical efficacy of intravitreal injection of ranibizumab in patients with ocular fundus diseases and changes in blood rheology.

First, we compared the intraocular pressure and visual acuity of the two groups of patients after treatment. The results showed that the visual acuity recovery and intraocular pressure recovery of the observation group were better than those of the control group (P<0.05). Subsequent efficacy comparisons also showed that the total effective rate of the observation group was significantly higher than that of the control group (P<0.05). This suggested that intravitreal injection of ranibizumab had a good effect in patients with ocular fundus diseases. Previous studies [21] have shown that ranibizumab can effectively reduce retinal edema in patients after injection into the eye. This can help to promote the recovery of vision and intraocular pressure in patients, which confirmed and explained our conclusions.

Then, the plasma viscosity, red blood cell aggregation index, and red blood viscosity index, as well as changes in PSV, EDV, and RI, were compared between the two groups of patients before and 1 week after treatment. The results showed that the plasma viscosity, red blood cell aggregation index and red blood viscosity index of the two groups were improved compared with those before treatment. However, the plasma viscosity, red blood cell aggregation index and red blood viscosity index of the observation group improved more significant than those of the control group (P<0.05). The

Table 4. Postoperative complications in both groups [n, (%)]

Complication	Observation group n=39	Control group n=39	X^2	P
Increased intraocular pressure	1 (2.56)	3 (7.69)	1.054	0.305
Intraocular infection	0	2 (5.13)	2.053	0.152
Retinal bleeding	1 (2.56)	4 (10.26)	1.923	0.166
Hard exudation	0	2 (5.13)	2.053	0.152
Total incidence	2 (5.13)	11 (28.21)	7.477	<0.050

Table 5. Quality of life one month after the operation in the two groups

Project	Observation group n=39	Control group n=39	t	P
Role function	81.66±3.55	71.79±2.57	14.06	<0.001
Physical function	82.33±3.19	72.47±2.98	14.11	<0.001
Emotional function	82.91±3.20	72.61±3.09	14.46	<0.001
Cognitive function	81.29±3.19	71.59±3.17	13.47	<0.001
Social function	80.79±3.36	71.48±2.93	13.04	<0.001

PSV, EDV and RI of the two groups were also improved compared with those before treatment. However, the PSV and EDV of the observation group were significantly higher than those of the control group, and the RI was significantly lower than that of the control group ($P<0.05$). The above results suggested that ranibizumab had a significant effect on the improvement of hemodynamics in patients with ocular fundus diseases. Some studies [22] explained the mechanism of ranibizumab to improve ocular fundus hemodynamics, saying that by antagonizing neovascularization in ocular fundus lesions, ranibizumab inhibited oozing edema of the blood vessels, thereby improving hemodynamics.

Then, the complications of the two groups of patients and the quality of life of the patients after one month of treatment were also compared. The results showed that the incidence of complications in the observation group was significantly lower than that in the control group ($P<0.05$), and the quality of life scores of the observation group were significantly higher than those in the control group after 1 month of treatment ($P<0.05$). This suggested that the intravitreal injection of ranibizumab had a high safety and can significantly improve the quality of life of patients. Previous studies [23] also indicated that intravitreal injection of ranibizumab was less likely to have adverse effects on the eye or system, which is also evidenced by our conclusions. Other studies [24] have shown that even simple intravitreal injection of ranibizumab will significantly reduce the leakage of choroidal neovascularization in patients with ocular fundus diseases, thereby improving vision without adverse reactions, which confirmed our conclusions from the side.

In summary, vitreous injection of ranibizumab has a relatively significant effect on patients with ocular fundus disease, and can effectively improve the hemodynamic indexes and life quality of patients with high safety, which is worthy of clinical application. However, in this study, the mechanism of action of ranibizumab was further explored and only one drug control was performed. In future studies, we will further explore the mechanism of action of ranibizumab in ocular fundus diseases, and further expand the sample size for multi-drug control, in order to provide more solutions for the treatment of ocular fundus diseases.

Acknowledgements

The authors received no financial support for the research, authorship, and/or publication of this article.

Disclosure of conflict of interest

None.

Address correspondence to: Zhinan Liu, Department of Ophthalmology, Changzhou Third People's Hospital, No. 300, Lanling North Road, Tianning District, Changzhou 213000, Jiangsu, China. Tel: +86-0519-82008315; E-mail: zhinanl@163.com

References

[1] Editors PO. Retraction: a novel image recuperation approach for diagnosing and ranking retinopathy disease level using diabetic fundus image. PLoS One 2017; 12: e0181891.

[2] Hirooka K, Saito W, Namba K, Mizuuchi K, Iwata D, Hashimoto Y and Ishida S. Early post-treatment choroidal thickness to alert sunset glow fundus in patients with Vogt-Koyanagi-Harada disease treated with systemic corticosteroids. PLoS One 2017; 12: e0172612.
[3] Morita C, Sakata VM, Rodriguez EE, Abdallah SF, Lavezzo MM, da Silva FT, Machado CG, Oyamada MK, Hirata CE and Yamamoto JH. Fundus autofluorescence as a marker of disease severity in Vogt-Koyanagi-Harada disease. Acta Ophthalmol 2016; 94: e820-e821.
[4] Yung M, Klufas MA and Sarraf D. Clinical applications of fundus autofluorescence in retinal disease. Int J Retina Vitreous 2016; 2: 12.
[5] Su J, Ao MX and Wang WJ. Application of color vision tests on the diagnosis and treatment for common ocular fundus diseases. International Eye Science 2016.
[6] Guo B, Wang L and Fan QH. The view of holistic integrated medicine in the development of diagnosis and treatment of ocular fundus diseases. Ophthalmology, Department Of J Negative 2016.
[7] Group CR, Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL and Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011; 364: 1897-1908.
[8] Iacono P, Parodi MB, Papayannis A, Kontadakis S, Sheth S, Cascavilla ML, Bandello F. Intravitreal ranibizumab versus bevacizumab for treatment of myopic choroidal neovascularization. Retina 2016; 32: 1539-1546.
[9] Zuo C, Zhang X, Li M, Peng Y, Mi L, Liu B and Wen F. Case series of coexistence of polypoidal choroidal vasculopathy with other rare fundus diseases. Int Ophthalmol 2019; 39: 987-990.
[10] Zhou Y and Wang M. [Development of en face optical coherence tomography and its application in ocular fundus diseases]. Zhonghua Yan Ke Za Zhi 2017; 53: 956-960.
[11] Kim J, Park KH and Woo SJ. Combined photodynamic therapy and intravitreal bevacizumab injection for the treatment of adult Coats' disease: a case report. Korean J Ophthalmol 2010; 24: 374-376.
[12] Kang H and Wang B. Hemodynamic effects of intravitreal injection of ranibizumab in patients with ocular fundus diseases. Department, Ophthalmology J China Medical Engineering 2017.
[13] Haroutounian S, Ratz Y, Ginosar Y, Furmanov K, Saifi F, Meidan R and Davidson E. The effect of medicinal cannabis on pain and quality-of-life outcomes in chronic pain: a prospective open-label study. Clin J Pain 2016; 32: 1036-1043.
[14] Vasconcelos-Santos DV, Sohn EH, Sadda S and Rao NA. Retinal pigment epithelial changes in chronic Vogt-Koyanagi-Harada disease: fundus autofluorescence and spectral domain-optical coherence tomography findings. Retina 2010; 30: 33-41.
[15] Cukras CA, Wong WT, Caruso R, Cunningham D, Zein W and Sieving PA. Centrifugal expansion of fundus autofluorescence patterns in Stargardt disease over time. Arch Ophthalmol 2012; 130: 171-179.
[16] Quellec G, Russell SR, Scheetz TE, Stone EM and Abramoff MD. Computational quantification of complex fundus phenotypes in age-related macular degeneration and Stargardt disease. Invest Ophthalmol Vis Sci 2011; 52: 2976-2981.
[17] Parodi MB, Iacono P, Sacconi R, Iuliano L and Bandello F. Fundus autofluorescence changes after ranibizumab treatment for subfoveal choroidal neovascularization secondary to pathologic myopia. Am J Ophthalmol 2015; 160: 322-327, e322.
[18] Menke MN, Framme C, Nelle M, Berger MR, Sturm V and Wolf S. Intravitreal ranibizumab monotherapy to treat retinopathy of prematurity zone II, stage 3 with plus disease. BMC Ophthalmol 2015; 15: 20.
[19] Guo YL, Du Y and He JF. Correlation between sunset glow fundus and initial dosage of corticosteroid in patients with Vogt-Koyanagi-Harada disease. Am J Ophthalmol 2009; 147: 946; author reply 946-947.
[20] Bai SJ. Efficacy of intravitreal ranibizumab or conbercept combined with laser photocoagulation for macular edema secondary to branch retinal vein occlusion. International Eye Science 2017.
[21] Rouvas AA, Ladas ID, Papakostas TD, Moschos MM and Vergados I. Intravitreal ranibizumab in a patient with choroidal neovascularization secondary to multiple evanescent white dot syndrome. Eur J Ophthalmol 2007; 17: 996-999.
[22] Lu Y, Huang J, Zhao J, Yu X, Long L and Dai H. Effects of intravitreal ranibizumab injection on Chinese patients with wet age-related macular degeneration: 5-year follow-up results. J Ophthalmol 2016; 2016: 6538192.
[23] Furino C, Boscia F, Cardascia N, Alessio G and Sborgia C. Hemorrhagic macular infarction after intravitreal bevacizumab for central retinal vein occlusion. Ophthalmic Surg Lasers Imaging 2010; 1-2.
[24] Bhatnagar P, Spaide RF, Takahashi BS, Peragallo JH, Freund KB, Klancnik JM Jr, Cooney MJ, Slakter JS, Sorenson JA and Yannuzzi LA. Ranibizumab for treatment of choroidal neovascularization secondary to age-related macular degeneration. Retina 2007; 27: 846-850.