• Clinical Research •

Clinical research of EX-PRESS drainage device and modified trabeculectomy combined with intravitreal conbercept treatment for neovascular glaucoma

Peng Li[1,2], Qing Liu[1], Xiao-Min Liu[1], Li Wang[3], Zhao-Jiang Du[4], Qian-Yan Kang[2]

[1]Department of Ophthalmology, Xijing 986 Hospital, Fourth Military Medical University, Xi'an 710054, Shaanxi Province, China

[2]Department of Ophthalmology, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, Shaanxi Province, China

[3]Ophthalmology Teaching and Research Section of Institute of Medical Technology, Xi'an Medical College, Xi'an 710032, Shaanxi Province, China

[4]Department of Ophthalmology, Xi'an Central Hospital, Xi'an 710001, Shaanxi Province, China

Correspondence to: Peng Li. Department of Ophthalmology, Xijing 986 Hospital, Fourth Military Medical University, Xi'an 710054, Shaanxi Province, China. drlipeng@126.com

Received: 2021-04-19 Accepted: 2021-09-17

Abstract

● **AIM:** To evaluate the efficacy and safety of modified trabeculectomy (experimental group) and implantation of EX-PRESS drainage device (control group), combined with intravitreal conbercept injection for neovascular glaucoma (NVG).

● **METHODS:** Totally 30 patients with NVG were selected from June 2014 to June 2017, and randomly divided into experimental group and control group. All patients were underwent intravitreal conbercept (0.5 mg/0.05 mL) treatment before surgery. Modified trabeculectomy was performed in MT group, while EX-PRESS drainage device implantation was performed in EX group. The success rates, best corrected visual acuity (BCVA), intraocular pressure (IOP), filtering bleb and complications were observed and compared.

● **RESULTS:** The differences of success rate, BCVA and filtering bleb were not statistically significant 12mo after the surgery (P>0.05), however, the difference of IOP at 1d, 1wk, 1, 3, and 6mo after surgery was statistically significant (F_{time}=390.64, P_{time}<0.0001) between two groups. The interactions between two groups in the given time showed no significant difference ($F_{intergroup\times time}$=0.181, $P_{intergroup\times time}$=0.57), and also there was no significant difference in IOP between the two groups (F=3.16, P=0.09). The results of pairwise comparison at each time point showed no significant difference in IOP between 1d and 1wk, 3 and 6, 3mo and 12mo after surgery (P>0.05), while the results at other time point indicate statistical differences (P<0.05).

● **CONCLUSION:** The modified trabeculectomy and the implantation of EX-PRESS drainage device have clinical application value in reducing IOP and postoperative complications of refractory NVG.

● **KEYWORDS:** modified trabeculectomy; EX-PRESS; conbercept; neovascular glaucoma

DOI:10.18240/ijo.2022.02.08

Citation: Li P, Liu Q, Liu XM, Wang L, Du ZJ, Kang QY. Clinical research of EX-PRESS drainage device and modified trabeculectomy combined with intravitreal conbercept treatment for neovascular glaucoma. *Int J Ophthalmol* 2022;15(2):242-247

INTRODUCTION

Neovascular glaucoma (NVG) is classified as a kind of secondary glaucoma. which is characterized by increased intraocular pressure (IOP), vision loss and severe pain. If the IOP becomes uncontrollable, cyclophotocoagulation and cryosurgery are used to avoid further optic nerve damage, but these surgical treatments associated with numerous risks that impairs the quality of patients' life. All kinds of diseases that can lead to fundus ischemia may lead to NVG. The most common conditions associated with NVG are diabetic retinopathy (DR), central retinal vein occlusion (CRVO), ocular ischemic syndrome (OIS). The pathogenesis of NVG includes passage of angiogenic factors [such as vascular endothelial growth factor (VEGF)] into the anterior segment that can lead to neovascularization. Iris neovascularization occurs after ischemic change of posterior segment of the eye. The IOP is generally not high initially, and then the neovascular grows into the anterior chamber angle, and the fibrous vascular membrane involves the trabecular meshwork, which blocks the aqueous humor circulation, increases the IOP, and reaches the stage of open angle glaucoma. In this stage,

drugs for lowering IOP and anti-VEGF can be used. When the disease develops further, the contraction of fibrovascular membrane pulls the iris, causing the chamber angle to close further, the iris pigment in the pupil area to evert, and the pupil to enlarge, leading to the angle-closure glaucoma[1]. The IOP lowering drugs and local treatment are difficult to be effective at this stage and surgical intervention is required. The effective control of IOP, saving patients' vision as much as possible and relieving patients' discomfort are the keys of treatment[2]. At present, NVG is a kind of refractory glaucoma, with its treatment still a challenge in ophthalmology. Simple trabeculectomy has no obvious effect of lowering IOP and may generate many complications, while surgery on ciliary body may cause irreversible IOP reduction and eyeball atrophy. Meanwhile, using drugs alone has limited therapeutic effect and is prone to relapse. Studies have shown that anti-VEGF drugs induce rapid regression of neovascularization, which can provide more time to allow other treatments to work[3]. Anti-VEGF drug injection combined with EX-PRESS drainage device implantation can be used for patients with NVG in order to maintain the ideal IOP level and protect the visual function[4-8]. In this study, modified trabeculectomy and EX-PRESS drainage device implantation were used separately after intravitreal injection of anti-VEGF drug Conbercept to evaluate the efficacy for patients with NVG.

SUBJECTS AND METHODS

Ethical Approval This study adhere to the principles of Declaration of Helsinki and was approved by the ethics boards of Xijing 986 Hospital. Written informed consent was obtained from all patients.

This was a prospective study. We reviewed the cases of 30 NVG patients from Department of Ophthalmology of Xijing 986 Hospital between June 2014 and June 2017. According to randomly divided into experimental group (16 eyes of 16 patients) and control group (14 eyes of 14 patients). All patients were underwent intravitreal conbercept (0.5 mg/0.05 mL) treatment for 7d before surgery, the experimental group was performed modified trabeculectomy, while the control group was performed EX-PRESS drainage device implantation. The patients were aged 28-55y, with the mean age of 39.90±8.31y.

The inclusion criteria were as follows: 1) diagnosis of NVG caused by diabetes mellitus (DM) or retinal vein occlusion; 2) aging from 18 to 60 years old; 3) only one eye per patient was included.

Exclusion criteria included: 1) patients with cataract; 2) with a personal history of trauma; 3) with unstable patients or those with severe comorbidities (*e.g.* cardiovascular diseases or hematological diseases) who cannot tolerate surgery; 4) has a history of ophthalmic surgery. There was no statistically significant difference between experimental group and control group in demographic data of patients (P>0.05; Table 1).

Table 1 Baseline characteristics of participants at preoperative

Characteristics	Experimental group	Control group	P
Age (y)	39.31±7.84	40.57±8.68	1.326
Gender	16	14	0.500
Female	4	4	
Male	12	10	
BCVA	1.23 ±0.39	1.10 ±0.42	0.182
IOP	45.63±6.50	45.93±5.61	3.443

BCVA: Best corrected visual acuity; IOP: Intraocular pressure.

Surgical Procedure

Intravitreal conbercept treatment After topical anesthesia, disinfection, sterile draping, and insertion of a speculum under the lid, 0.5 mg/0.05 mL of conbercept (Chengdu Kanghong Bio technologies Co., Ltd., China) was injected into the vitreous body using a 29G needle at 3.5 mm limbus. After injection of conbercept, pressing with cotton bud, and apply antibiotic gel to the wound and bandage it. All patients were receiving surgery treatment when disappearance of iris neovascularization after intravitreal injection.

The experimental group was performed modified trabeculectomy. Anesthesia was obtained by oxybuprocaine hydrochloride eye drops. After anesthesia, a fornix-based bulbar conjunctival (5×5 mm^2) and lamellar scleral flap (4×4 mm^2) were created, and put the 5-fluorouracil (5-FU) cotton piece on scleral flap stroma bed. Making a deep scleral flap (3×2 mm^2) from the separated scleral bed, and separate to corneoscleral limbus and cut off, then incision the trabecular on both sides and cut off the corresponding position of iris tissue. The surgical procedure of modified trabeculectomy was shown in Figure 1.

The control group was treated with implantation of EX-PRESS glaucoma drainage device P50 (ALCON). A 25G needle was used to penetrate horizontally into the anterior chamber at the transparent cornea along the scleral flap, and the introducer entered the anterior chamber along the puncture site, parallel to the iris. After rotating, the EX-PRESS glaucoma drainage device was implanted and fixed (Figure 2).

Tenon's capsule was closed with 10-0 nylon interruptedly and the conjunctiva was closed by continuous running suture. Antibiotic eye ointment was coated in conjunctival sac, and sterile dressing is exploited to bind the surgical eyes. All the operations were performed by the same ophthalmologist. After corneal transparency, all the patients were treated with panretinal photocoagulation.

Outcome and Analysis Postoperative IOP was obtained at 1d, 1wk, 1, 3, 6, and 12mo. The success rate between two groups at 12mo postoperative, and IOP, BCVA, filtration bleb and complications were observed. Criteria for success rate were included complete success, partial success and fail. Complete success was defined as an IOP<21 mm Hg without

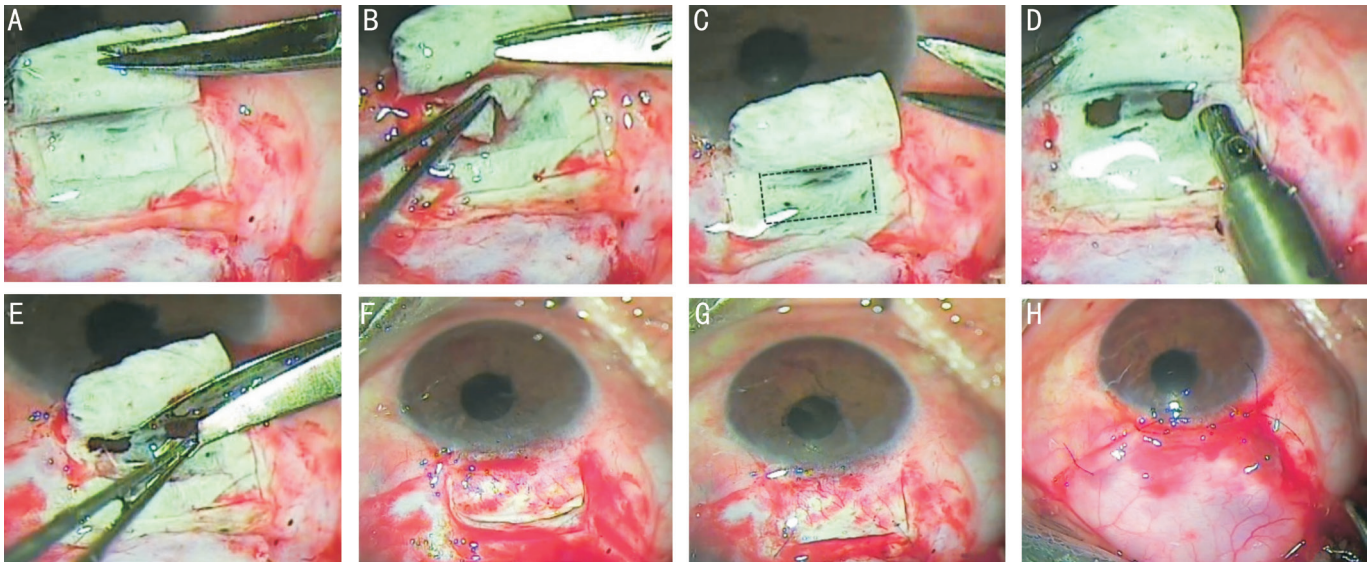

Figure 1 Modified trabeculectomy A: Creation of a 3×2 mm^2 deep-thickness scleral flap; B: Cut off the deep scleral flap; C: Thin iris tissue; D: Cut off the trabecular on both sides; E: Cut off the iris tissue; F: Reduction of lamellar scleral flap; G: Suture of scleral flap; H: Bulbar conjunctiva was sutured, with obvious filtration bleb.

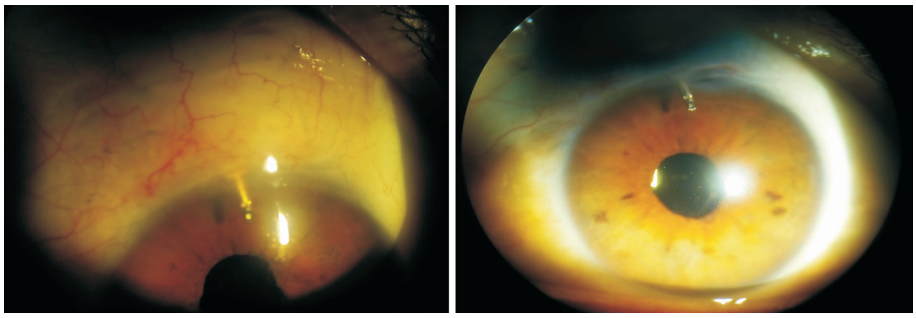

Figure 2 Anterior segment photography after EX-PRESS glaucoma drainage device implantation surgery.

use of additional glaucoma medicines, and no complications. Partial success was defined as an IOP<21 mm Hg with the use of glaucoma medicines, no severe complications. Failure was defined as an IOP>21 mm Hg despite the use of glaucoma medicines, or requiring another glaucoma surgical intervention, with severe complications.

Shapes of filtering bleb are observed slit lamp microscope and classified according to Krofeld classification method. Micro-cystic type was Type I, diffuse flat type was Type II, absent type was Type III, and wrapped type was Type IV. The functional filtering blebs are Type I and Type II, and the non-functional filtering blebs are Type III and Type IV. Type I and type II filtering blebs are functional and successful filtering blebs.

Statistical Analysis The data were processed and statistically analyzed using SPSS version 18.0. All the data were expressed as mean±standard deviation (SD). Baseline characteristics and outcome variables were using the Student's *t*-test or one-way ANOVA. Chi-square test was used to compare the composition ratio between the two groups. Mann-Whitney *U* test was used for visual improvement between the two groups. The value of $P<0.05$ was considered to be statistically significant.

RESULTS

Success Rate The operation success rate was 75% in experimental group, and it was 85.7% in control group, $\chi^2=0.54$. ($P=0.46$; Table 2).

Best Corrected Visual Acuity There was no significant difference in BCVA between the experimental group and the control group 12mo after operation ($t_{experiment}=-0.93$, $P_{experiment}=0.37$; $t_{control}=-0.17$, $P_{control}=0.87$), and there was no significant statistical difference in visual improvement between the two groups 12mo after operation ($U=110.0$, $P=0.98$; Table 3).

Intraocular Pressure Repeated measures ANOVA showed that the IOP at each time point was statistically significant ($F_{time}=390.64$, $P_{time}<0.0001$). There was no significant statistical difference in the interaction between each time point and the groups ($F_{intergroup\times time}=0.181$, $P_{intergroup\times time}=0.57$). The statistical difference in IOP was not significant between the experimental group and the control group ($F_{intergroup}=3.16$, $P_{intergroup}=0.09$).

The results of pairwise comparison at each time point showed that there were no significant differences in IOP between 1d and 1wk after operation, 3mo and 6mo after operation, 3mo and 12mo after operation ($P>0.05$), but differences were

Table 2 Comparison of the success rate between two groups at 12mo postoperative *n* (%)

Groups	*n*	Complete success	Partial success	Fail	Success rate
Experimental group	16	8 (50)	4 (25.0)	4 (25)	12 (75)
Control group	14	9 (64.3)	3 (21.4)	2 (14.3)	12 (85.7)

Table 3 Preop. and postop. BCVA levels in two groups and visual changes mean±SD, mm Hg; *n* (%)

Groups	*n*	Preop.	Postop. 12mo	Diminution of vision	Improvement of vision	Vision unchanged
Experimental group	16	1.23±0.39	1.17±0.40	3 (18.8)	5 (31.3)	8 (50.0)
Control group	14	1.10±0.42	1.06±0.38	3 (21.4)	5 (35.7)	6 (42.9)

Preop.: Preoperative; Postop.: Postoperative.

Table 4 Preop. and postop. IOP levels mean±SD, mm Hg

Groups	*n*	Preop.	Postop. 1d	Postop. 1wk	Postop. 1mo	Postop. 3mo	Postop. 6mo	Postop. 12mo
Experimental group	16	45.63±6.50	9.44±1.32	9.38±1.54	11.81±1.47	16.56±2.57	16.94±2.05	17.94±6.15
Control group	14	45.93±5.61	9.64±1.44	10.21±1.61	14.71±2.71	19.00±2.92	18.29±1.87	17.86±4.69

Preop.: Preoperative; Postop.: Postoperative.

Table 5 Comparison of the filtration bleb between two groups at 12mo postoperative *n* (%)

Groups	*n*	Functional filtration bleb		Nonfunctional filtration bleb	
		I	II	III	IV
Experimental group	16	7 (43.8)	6 (37.5)	2 (12.5)	1 (6.3)
Control group	14	6 (42.9)	5 (35.7)	1 (7.1)	2 (14.3)

significant in statistics in pairwise comparison at other time points (P<0.05; Table 4).

Filtration Bleb The proportion of the functional filtration bleb in experimental group was 81.3%, and it was 18.8% in nonfunctional filtering blebs. There was no significant statistical difference in successful filtering blebs between the experimental group and the control group (χ^2=0.03, P=0.85; Table 5).

Complications No hyphema occurred during operations. The experimental group had 1 case of hyphema and 3 cases of shallow anterior chamber, and the control group had 1 case of malignant glaucoma, 1 case of hyphema and 1 case of shallow anterior chamber post-operation. There were no retinal and choroidal detachment in both groups. Complications of the two groups relieved after symptomatic treatment.

DISCUSSION

NVG has always been a tough problem in clinical treatment of ophthalmology. Neovascularization of iris makes the operation difficult to complete due to hyphema, leading to the failure of surgery[9]. The primary pathological basis of NVG is hypoxia[10].

In recent years, anti-VEGF drugs have been widely used in anti-glaucoma surgery[11]. Intravitreal injection of anti-VEGF drugs is exploited to inhibit the formation of neovascularization, so as to gradually subside the neovascularization of iris and chamber angles, and to improve the function of the trabecular meshwork, lowering IOP, creating a window period for glaucoma surgery[12]. Commonly used anti-VEGF drugs included pegaptanib, bevacizumab, ranibizumab, aflibercept, and conbercept. This study was using Conbercept for NVG surgery. Conbercept is an antibody-based genetically engineered drug, a VEGF receptor fusion protein, which has the advantages of multiple targets, strong affinity and long action time. Its structure is similar to VEGFTrap-EYE, but the former contains the IG-like region 4 (KDRD 4) in VEGFR-2 (KDR). Conbercept and VEGF can be tightly bound to penetrate the retina by enhancing the dimerization and modifying its three-dimensional structure. It can widely bind VEGF-A, VEGF-B and placental growth factor (PLGF), *etc*. Studies have shown that when treating choroidal neovascularization. Conbercept has a certain effect on eliminating choroidal neovascularization, making it atrophy, reducing liquid leakage and edema[5,13]. In this study, all cases were treated with anti-glaucoma surgery after anti-VEGF treatment and no secondary bleeding occurred to influence the operations.

In the current NVG treatment, the effect of drug treatment is poor, and that of the traditional anti-glaucoma surgery is also poor due to bleeding, inflammatory reaction and scaring of filtering channel[13-14]. IOP is easy to be out of control during the treatment. Studies have shown that human tenon fibroblasts (HTF) located in the surgical incision area play an important role in scar formation by promoting the proliferation, migration and synthesis of extracellular matrix. It also generates effects in resisting the metabolite 5-FU and preventing the

formation of scar tissue after surgery[15]. 5-FU is a pyrimidine antagonist, which is converted into 5-fluoro-2-deoxyuracil nucleotide *in vivo*, covalently binding with deoxythymidylate synthetase to interfere DNA synthesis. In addition, 5-FU can be incorporated into RNA after being converted *in vivo*, to interfere protein synthesis. Its specificity acts on the S phase of cell proliferation cycle[9-10]. Due to the current clinical shortage of mitomycin C (MMC), although applying 5-FU dressing to resist scar formation in this study, the miss of MMC dressing might be a factor, attributed to the partial-success and failure cases. The latest comparative study shows that the success rate of applying MMC is slightly higher than that of 5-FU, but there is no significant difference in safety[11].

As a successful glaucoma surgery, we hope that the conjunctival wound will heal well without leakage, but for scleral flap, adhesion and excessive healing will affect glaucoma filtration. In addition to the application of 5-FU, the modified glaucoma surgery is to make a deep scleral pool, with the aim of preventing the upper scleral flap from closely sticking to the lower scleral tissue as much as possible, Aqueous humor will be drained into the pool, and then slowly flowing through the new scleral cavity to the conjunctival filtering bleb, to form a new external drainage owing to the high permeability of ciliary body and choroid capillary endothelial system. Because trabeculectomy is double-holed, shallow anterior chamber is easy to appear after operation. Therefore, when surgery is finished, a little volume of viscoelastic agent is injected into the anterior chamber or making adjustable suturing of scleral flap. Two patients showed shallow anterior chamber within 1wk after the operations, but the anterior chamber is well formed and the IOP control is satisfying through gentle operating during operation and local pressure.

At present, the widely-used EX-PRESS glaucoma drainage device is made of metal, with good histocompatibility, and small size (2-3 mm in length, 50 or 200 μm in inner diameter and 0.4 mm in outer diameter). It is directly implanted into the anterior chamber through a puncture under the lamellar scleral flap, draining the aqueous humor to the inferior scleral space to control IOP. In the previous studies[12,16], it was considered that this operation was easy to conduct, leaving minimal wound and avoiding trabeculectomy and iridectomy. It also leads to minor inflammatory reaction and better IOP lowering, with few side effects. This study indicates that the success rate of surgery in the experimental group is 75%, while that in the control group is 85.7%, with no statistical difference (P>0.05). This also shows that our modified trabeculectomy has the same filtering effect as drainage device implantation.

In our study cases, pan retinal photocoagulation (PRP) treatment was performed after operation. One of the treatment methods of ischemia is to reduce the oxygen demand of retina by reducing the peripheral optical nonfunctional parts of retina. Therefore, inhibiting the neovascularization in anterior chamber angle and preventing the occurrence of NVG, are still the top treatment standard. Our research results manifest that the modified surgical methods with anti-VEGF, combined with PRP and “triple sequential therapy” have the same satisfactory IOP control rate[16-18].

In recent years, it has become a hot researching topic on how to control IOP of patients with NVG in a stable state for a long time or improve their visual function[19-21]. Therefore, some observation indexes of this study mainly target at the 12mo after surgery. Complications are the main cause of visual acuity decline in patients with NVG. VEGF will be released to the nearby intraocular tissues, which will be accompanied by aqueous humor circulating from the pupil to the angle of anterior chamber, where neovascularization will be generated, which causing the rise of IOP and corneal edema. This will become a vicious cycle. The results of this study showed that the BCVA of the two groups at 12mo after operation was not significantly different from that before operation and there was no significant difference between the two groups (P>0.05), which may be different from other studies. Because of the existence of double trabecular foramen and scleral cistern, continuous aqueous humor flow may reduce inflammation and scar formation, and can significantly reduce the occurrence of postoperative high IOP. The drainage device used in the control group also reduced IOP rapidly. Theoretically, methods adopted in both groups could make patients’ vision recover faster, however, due to the small number of cases, this study failed to achieve the expected improvement of visual function. In anti-glaucoma surgery, the formation of conjunctival filtering blebs is a sign of success. In our research, no significant statistical difference displayed in functional filtering bleb between the experimental group and the control group (P>0.05). The results of the two groups are basically consistent with the success rate of surgery, indicating that anti-glaucoma effects are both satisfying in two groups. We consider the success of filtering bleb is not necessarily positively correlated with the decrease of IOP in some NVG. In the control group of this study, P50 drainage device was used, but no specific analysis of its effect was made, and scar formation after NVG filtration was not analyzed either. In future studies, the research design should be further refined and summarized.

Postoperative complications of NVG surgery are very common. In this study, the postoperative complications of the two groups of patients relieved after symptomatic treatment, which also shows that the two groups have good curative effect.

At present, there are many ways to treat NVG. Trabeculectomy for NVG is common after intravitreal injection of Conbercept,

a kind of anti-VEGF drug[22]. Our research shows that in a certain period, the modified trabeculectomy with lower cost and the implantation of EX-PRESS drainage device have certain clinical application value for refractory NVG to reduce IOP and postoperative complications[23-24]. Regretfully, the number of research cases is limited, and the duration of observation is not long enough. Long term observation and summary from multicenters will still be required in the future.

ACKNOWLEDGEMENTS

Foundations: Supported by the Social Development Project of Shaanxi Provincial Department of Science and Technology (No.2020SF-167); General Social Scientific Research Plan Project of Shaanxi Provincial Education Department in 2021 (No.21JK0891); The Innovation and Entrepreneurship Program for College Students at Xi'an Medical College (No.121521113).

Conflicts of Interest: Li P, None; **Liu Q,** None; **Liu XM,** None; **Wang L,** None; **Du ZJ,** None; **Kang QY,** None.

REFERENCES

1 Barac IR, Pop MD, Gheorghe AI, Taban C. Neovascular secondary glaucoma, etiology and pathogenesis. *Rom J Ophthalmol* 2015;59(1):24-28.

2 Ma RJ, Lv P, Zhang WF. Different treatments and therapeutic evaluation of neovascular glaucoma. *Guoji Yanke Zazhi (Int Eye Sci)* 2018;18(12):2173-2178.

3 Havens SJ, Gulati V. Neovascular glaucoma. *Dev Ophthalmol* 2016;55:196-204.

4 Xie JB, Kou YH, Liu RP, Yang SS, Yue XD, Wang HX. EX-Press implantation combined with intravitreal injection of ranibizumab for neovascular glaucoma. *Rec Adv Ophthalmol* 2016;36(1):61-64.

5 Li P, Chen HY, Hai O, Wang L, Sun CH. Conbercept intravitreal injection combined with EX-PRESS glaucoma drainage device implantation for NVG. *Guoji Yanke Zazhi (Int Eye Sci)* 2019;19(7):1218-1221.

6 Han GJ, Zhou HZ, Zhang WQ, Huang ZJ, Yan M. Comparison of therapeutic effect in early stage between Ex-PRESS implantation and trabeculectomy for open angle glaucoma. *Rec Adv Ophthalmol* 2014;34(8):758-760.

7 Gao CW, Chen Wei, Yang XY. Clinical observation of Ex-Press glaucoma device implantation for neovascular glaucoma. *Rec Adv Ophthalmol* 2018;38(8):762-765.

8 Zhu Y, Li J, Xu SK. Therapeutic effects of Ex-PRESS glaucoma filtration device implantation in neovascular glaucoma. *Guoji Yanke Zazhi (Int Eye Sci)* 2015;15(3):534-536.

9 Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. *JAMA* 2014;311(18):1901-1911.

10 Andrés-Guerrero V, Perucho-González L, García-Feijoo J, Morales-Fernández L, Saenz-Francés F, Herrero-Vanrell R, Júlvez LP, Llorens VP, Martínez-de-la-Casa JM, Konstas AGP. Current perspectives on the use of anti-VEGF drugs as adjuvant therapy in glaucoma. *Adv Ther* 2017;34(2):378-395.

11 Simha A, Braganza A, Abraham L, Samuel P, Lindsley K. Anti-vascular endothelial growth factor for neovascular glaucoma. *Cochrane Database Syst Rev* 2013(10):CD007920.

12 Shinohara Y, Akiyama H, Magori M, Kishi S. Short-term outcomes after EX-PRESS implantation versus trabeculectomy alone in patients with neovascular glaucoma. *Clin Ophthalmol* 2017;11:2207-2213.

13 Sun YY, Liang Y, Zhou P, Wu HJ, Hou XR, Ren ZQ, Li XX, Zhao MW. Anti-VEGF treatment is the key strategy for neovascular glaucoma management in the short term. *BMC Ophthalmol* 2016;16(1):150.

14 Wang MH, Li QM, Dong HT, Dong SQ, Li Y, Zheng CY. Ahmed valves vs trabeculectomy combined with pans plana vitrectomy for neovascular glaucoma with vitreous hemorrhage. *Eur J Ophthalmol* 2017;27(6):774-780.

15 Nakatake S, Yoshida S, Nakao S, Arita R, Yasuda M, Kita T, Enaida H, Ohshima Y, Ishibashi T. Hyphema is a risk factor for failure of trabeculectomy in neovascular glaucoma: a retrospective analysis. *BMC Ophthalmol* 2014;14:55.

16 Mariotti C, Dahan E, Nicolai M, Levitz L, Bouee S. Long-term outcomes and risk factors for failure with the EX-PRESS glaucoma drainage device. *Eye* (*Lond*) 2014;28(1):1-8.

17 Ogura S, Yasukawa T, Kato A, Kuwayama S, Hamada S, Hirano Y, Uemura A, Yoshida M, Ogura Y. Indocyanine green angiography-guided focal laser photocoagulation for diabetic macular edema. *Ophthalmologica* 2015;234(3):139-150.

18 Sebag J, Nguyen-Cuu J. The effects of vitreous on proliferative diabetic retinopathy and the response to pan retinal photocoagulation. *Graefes Arch Clin Exp Ophthalmol* 2017;255(2):421-422.

19 Nikkhah H, Ghazi H, Razzaghi MR, Karimi S, Ramezani A, Soheilian M. Extended targeted retinal photocoagulation versus conventional pan-retinal photocoagulation for proliferative diabetic retinopathy in a randomized clinical trial. *Int Ophthalmol* 2018;38(1):313-321.

20 Hong Y, Hu YT, Dou HL, Wang CG, Zhang C, Ma ZZ. Comparison of the safety and efficacy of triple sequential therapy and transscleral cyclophotocoagulation for neovascular glaucoma in the angle-closure stage. *Sci Rep* 2018;8(1):7074.

21 Fukuda S, Beheregaray S, Kasaragod D, Hoshi S, Kishino G, Ishii K, Yasuno Y, Oshika T. Noninvasive evaluation of phase retardation in blebs after glaucoma surgery using anterior segment polarization-sensitive optical coherence tomography. *Invest Ophthalmol Vis Sci* 2014;55(8):5200-5206.

22 Villamarin A, Stergiopulos N, Bigler S, Mermoud A, Moulin A, Roy S. *In vivo* testing of a novel adjustable glaucoma drainage device. *Invest Ophthalmol Vis Sci* 2014;55(11):7520-7524.

23 Wubben TJ, Johnson MW, Anti-VEGF Treatment Interruption Study Group. Anti-vascular endothelial growth factor therapy for diabetic retinopathy: consequences of inadvertent treatment interruptions. *Am J Ophthalmol* 2019;204:13-18.

24 Zhang XL. Could Ex-PRESS miniature implantation replace the trabeculectomy in China? *Chin J Exp Ophthalmol* 2015;33:193-195.