• Clinical Research •

Short-term fluctuation of intraocular pressure and influencing factors following intravitreal injection in patients with retinal vascular diseases

Jing-Peng Miao, Yi-Yun Zeng, Xin-Ming Gu, Xin-Yuan Zhang

Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing Institute of Ophthalmology, Beijing Key Laboratory of Institute of Ophthalmology and Visual Sciences, Beijing 100730, China

Co-first authors: Jing-Peng Miao and Yi-Yun Zeng

Correspondence to: Xin-Yuan Zhang. Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing Institute of Ophthalmology, Beijing Key Laboratory of Institute of Ophthalmology and Visual Sciences, Beijing 100730, China. mmzxy2010@163.com

Received: 2024-04-07 Accepted: 2024-07-29

Abstract

● **AIM:** To investigate the patterns of short-term intraocular pressure (IOP) fluctuations and identify the contributing factors following intravitreal injection in patients with retinal vascular diseases.

● **METHODS:** Totally 81 patients were enrolled in this case control study. Eyes were categorized into 7 groups, including age-related macular degeneration (AMD), polypoidal choroidal vasculopathy (PCV), idiopathic choroidal neovascularization (CNV), proliferative diabetic retinopathy (PDR), diabetic macular edema (DME), macular edema secondary to branch (BVOME) and central (CVOME) retinal vein occlusion. IOP was measured in all patients using rebound tonometer at 7 preset time points perioperatively. Additionally, based on the administered medication, the eyes were classified into three treatment groups, including dexamethasone intravitreal implant (IVO), intravitreal conbercept (IVC), and intravitreal ranibizumab (IVR). To compare IOP values at various time points across groups, we employed one-way ANOVA, independent sample *t*-test or χ^2 test and multivariate logistic regression analysis.

● **RESULTS:** Peak IOP values across all groups were observed at 40s, and 5min after intravitreal injection. Statistical differences in IOP were detected at the 5min among the 7 indication groups (F=2.50, P=0.029). When examing the impact of medications, the IVO group exhibited lower average IOP values at both 40s and 5min compared to the IVC and IVR groups (P<0.001; P=0.007). The IOP values at 40s and 5min were significantly higher in BVOME and CVOME group compared to non-retinal vein occlusion-secondary macular edema (RVOME) group (P<0.001). Multivariate logistic regression analysis further confirmed that IOP measurement at 40s was significantly higher in CVOME group than in non-RVOME group (OR=1.64, 95%CI: 1.09-2.47; P=0.018).

● **CONCLUSION:** Needle size plays a crucial role in the transient changes of IOP following intravitreal injection. Before administering intravitreal injection to patients with central retinal vein occlusion, it is essential to exclude any underlysing causes of increased IOP.

● **KEYWORDS:** intravitreal injection; rebound tonometer; intraocular pressure; retinal vein occlusion; ocular fundus diseases

DOI:10.18240/ijo.2024.11.11

Citation: Miao JP, Zeng YY, Gu XM, Zhang XY. Short-term fluctuation of intraocular pressure and influencing factors following intravitreal injection in patients with retinal vascular diseases. *Int J Ophthalmol* 2024;17(11):2052-2059

INTRODUCTION

The intravitreal injection has emerged as one of the most commonly utilized methods for the treatment of the posterior segment of ocular diseases due to its advantages of immediate and increased therapeutic effect in the intended retinal target tissue. Since the approval of anti-vascular endothelial growth factor (anti-VEGF) agents in 2006, the utilization of intravitreal injections for treating retinal and choroidal vascular diseases, including wet age-related macular degeneration (wAMD), diabetic macular edema (DME), retinal vein occlusion-secondary macular edema (RVOME) and idiopathic macular neovascularization, has rapidly increased annually[1].

Despite the well-recognized safety of intravitreal injections, transience elevation of intraocular pressure (IOP) post-injection is a common phenomenon and frequently overlooked

by clinicians[2]. A Meta-analysis has confirmed that the long-term reduction in retinal nerve fiber layer (RNFL) thickness and development of glaucomatous optic nerve damage in patients following intravitreal injection may be associated with IOP fluctuations[3]. Transient IOP elevation following intravitreal injection may be attributed to a transient elevation in intravitreal contents and transient angle closure resulting from the anterior iridal septum. However, the potential risk factors remain unknown.

This study investigated the short-term fluctuations in IOP in patients with various retinal vascular diseases, but without glaucoma, following intravitreal injections. By measuring IOP in a sitting position using rebound tonometer both before and after injections, we explored the patterns of short-term IOP changes across different clinical conditions and additional factors. This study aims to offer more substantial evidence to inform clinical practice.

SUBJECTS AND METHODS

Ethical Approval The study protocol was approved by the Medical Ethics Committee of Beijing Tongren Hospital, affiliated to Capital Medical University (No.TREC2023-KY018). The patients written informed consent obtained before undergoing any examinations.

General Materials This case-control study enrolled 81 patients (81 eyes) who underwent intravitreal injection at Beijing Tongren Hospital from June 2020 to June 2021. Totally 36 males (36 eyes), and 45 females (45 eyes), with an average age of 56.27±13.24y (range, 16-83y) were recruited.

Inclusion and Exclusion Criteria The inclusion criteria for the study are : 1) diagnosis of age-related macular degeneration (AMD), polypoidal choroidal vasculopathy (PCV), choroidal neovascularization (CNV), DME, proliferative diabetic retinopathy (PDR), branch retinal vein occlusion macular edema (BVOME) and central retinal vein occlusion macular edema (CVOME); 2) no prior history of intravitreal injections before enrollment; 3) baseline IOP below 22 mm Hg without the use of IOP-lowering medications; 4) comprehensive ophthalmic examination records available; 5) provision of voluntary, written informed consent; 6) in cases where both eyes meet the inclusion criteria, one eye is randomly selected for the study.

The exclusion criteria for the study are: 1) refractive errors exceeding ±3 D in the operative eye; 2) history of IOP over 21 mm Hg in the operative eye, or a diagnosis of intraocular hypertension; 3) any form of glaucoma diagnosis or prior treatment with IOP-lowering medication; 4) patients with a family history of glaucoma; 5) keratopathy affecting IOP measurement; 6) recent oral or intraocular hormone therapy; 7) surgical history in the operative eye; 8) an anterior chamber angle depth graded 1 by the van Herick ratio, or angle closure in any of the four quadrants as determined by ultrasound biomicroscope (UBM); 9) significant lens capsule damage or opacification post-surgery; 10) inability to complete IOP measurements at required times before and after intravitreal injection; 11) patients with two or more specified inclusion diesases.

Patient Grouping Based on the indications for intravitreal injection, participants' eyes were categorized into seven groups, including AMD, PCV, CNV, PDR, DME, BVOME, and CVOME groups. Based on the type of drug used for intravitreal injection, the eyes were categorized into three groups: the dexamethasone intravitreal implant group (IVO group), the intravitreal conbercept group (IVC group), and intravitreal ranibizumab group (IVR group). After excluding the IVO group, classification was further refined by age (≤60 or >60y), gender, and indication which included the BVOME group, the CVOME group and the non-RVOME group.

Injection Agents The substances used for injections were ranibizumab (Novartis, Switzerland), conbercept (Chengdu Kanghong Biological Co., Ltd., Chengdu, China) and dexamethasone intravitreal implant (Bayer, Germany).

Surgical Procedure of Intravitreal Injection Three days before the surgery, gatifloxacin eye gel (Shenyang Xingqi Eye Medicine Co., Ltd., China) was applied four times per day. During the operation, 0.5% proparacaine hydrochloride eye drops (Alcon Company, USA) were instilled for topical anesthesia, followed by routine disinfection. The conjunctival sac was sterilized using 0.5% povidone-iodine (Shanghai Likang Disinfection High-tech Co., Ltd., China) for 30s, followed by a rinse with 0.9% saline. After locating the appropriate site, the needle was inserted either 4.0 or 3.5 mm posterior to the limbus (aphakic eye). For the injection of ranibizumab and conbercept, a 30-gauge (G) needle was employed, delivering a single dose of 0.05 mL. The bulbar conjunctiva at the injection site was gently separated using a cotton swab, allowing for the slow injection of the drug into the vitreous cavity. Prior to injecting the dexamethasone intravitreal implant, the bulbar conjunctiva at the site was parted using either a microscopic tooth forceps or a sterile cotton swab. This step was followed by the use of a 22G needle, acting as a scleral canal, through which the dexamethasone implant was vertically injected into the vitreous cavity. After the injection, the site was pressed with a cotton swab for 5s to prevent any reflux of vitreous fluid or medication.

Routine Eye Examinations All subjects underwent a comprehensive eye examination, including visual acuity and best corrected visual acuity (Snellen vision) examination, slit-lamp microscopy (BM900 slit-lamp microscope, Haag-

Table 1 Baseline characteristics of enrolled patients

Parameters	AMD (*n*=14)	PCV (*n*=3)	CNV (*n*=7)	PDR (*n*=11)	DME (*n*=22)	BVOME (*n*=15)	CVOME (*n*=9)	Total (*n*=81)
Age, y	67.00±8.72	65.00±4.58	43.43±20.75	57.91±12.90	55.59±10.06	57.00±11.25	49.89±13.55	56.80±13.24
Gender (female/male)	9/5	2/1	5/2	8/3	7/15	8/7	6/3	45/36
Type of agents (IVO/non-IVO)	0/14	0/3	0/7	0/11	1/21	4/11	1/8	6/75
Preop. IOP, mm Hg	14.22±1.60	15.53±1.33	17.16±2.40	15.66±1.77	15.49±1.98	15.93±2.06	15.07±2.17	15.47±2.02
Postop. IOP at 40s, mm Hg	45.21±9.00	45.73±2.93	48.11±10.73	44.36±7.49	42.75±9.45	46.26±20.84	53.72±16.01	45.84±12.83
Postop. IOP at 5min, mm Hg	23.99±7.17	22.10±1.87	27.50±6.44	22.79±5.12	25.33±4.40	29.17±8.41	30.71±6.41	26.13±6.62
Postop. IOP at 15min, mm Hg	18.46±5.68	18.60±1.99	21.23±5.33	18.15±2.84	18.69±2.47	19.51±3.64	21.29±5.76	19.23±4.11
Postop. IOP at 30min, mm Hg	17.03±4.79	18.13±0.40	19.50±3.40	17.00±2.54	17.11±2.57	17.89±2.11	18.96±5.47	17.67±3.41
Postop. IOP at 1h, mm Hg	16.50±4.11	17.07±0.55	18.39±2.98	16.20±1.83	16.15±2.29	17.01±2.00	18.04±4.14	16.81±2.86
Postop. IOP at 1d, mm Hg	14.28±1.32	14.70±0.78	16.96±2.85	15.23±1.72	15.00±1.99	15.40±1.79	15.01±2.32	15.14±1.97

AMD: Age-related macular degeneration; PCV: Polypoidal choroidal vasculopathy; CNV: Choroidal neovascularization; PDR: Proliferative diabetic retinopathy; DME: Diabetic macular edema; BVOME: Branch retinal vein occlusion macular edema; CVOME: Central retinal vein occlusion macular edema; IVO: Dexamethasone intravitreal implant; IOP: Intraocular pressure.

Streit, Switzerland), fundus examination (Omega500 binocular indirect ophthalmoscope, HEINE, Germany) after pupillary dilation with compound topicamide eye drops (Santen Pharmaceutical Co., Ltd., Japan), fundus photochromy (CR-1 non-mydriatic fundus camera, Canon Co., Ltd., Japan), swept-source optical coherence tomography (OCT; DRI OCT-1 Atlantis scanner, Topcon Co., Ltd., Japan), optical coherence tomography angio-graphy (OCTA; RTVue XR Fourier OCTA, Optovue, USA), UBM (AVISO Ultrasonic ophthalmology diagnostic instrument, Quantel Medical, France) for checking the risk of angle-closure glaucoma in subjects.

IOP measurements were consistently performed by the same clinician using the identical rebound tonometer (Icare PRO handheld rebound tonometer, Icare, Finland) at 7 preset time points, including baseline (T0) and 40s (T1), 5min (T2), 15min (T3), 30min (T4), 60min (T5), and 1d (T6) post injection. In the operative eye, IOP was measured at the central cornea with the patient in an upright sitting position, using the lateral eye as a control. The rebound tonometer, a portable device consisting of a magnetic probe and a solenoid, operates within a 3 to 7 mm working distance from the cornea. The patient's forehead serves as the support base, allowing for adjustment of the probe's distance to the cornea. Upon activating the measurement button, an electric pulse generates a magnetic field, propelling the probe toward the cornea and back, facilitating IOP calculation[4]. This study utilized six consecutive measurements, automatically discarding the highest and lowest values to compute the average of IOP. A green screen variation indicated a standard deviation within the normal range; otherwise, measurements were repeated until achieving a standard deviation within the desired range. The final average IOP was documented for further analysis.

Statistical Analysis Statistical analysis was performed using SPSS 25.0 (IBM, Chicago, Illinois, USA). The Shapiro-Wilk test assessed the normal distribution of continuous variables, including age and IOP at various time points. Data following a normal or approximately normal distribution were presented as the mean±standard deviation. The Levene test confirmed the variance homogeneity of the data between groups. One-way ANOVA compared the IOP values at different time points among these groups. Based on data types, the independent sample *t*-test or χ^2 test was used to compare IOP values at different time points among the operative eyes, excluding the IVO group. Multivariate logistic regression analysis, adjusted for age, gender and other factors, compared IOP values across the BVOME, CVOME, and non-RVOME groups. $P<0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics A total of 81 subjects (81 eyes) were included in this study. Eyes were categorized into seven groups according to the indications which were the AMD, PCV, CNV, PDR, DME, BVOME, and CVOME groups. The neovascular age-related macular degeneration (nAMD) group included 14 subjects with an average age of 67.00±8.72y, 3 subjects were in PCV group with an average age of 65.00±4.58y, 7 subjects were in idiopathic CNV group, with an average age of 43.43±20.75y, 11 subjects (all males) in PDR group, with an average age of 57.91±12.90y, 22 subjects in DME group, with an average age of 55.59±10.06y, 15 subjects (11 males, 4 females) in BVOME group, with an average age of 57.00±11.25y and 9 subjects in CVOME group, with an average age of 49.89±13.55y (rang, 33-68 y). The data are shown in Table 1.

After analyzing the IOP across the seven groups based on disease category indications, 40.74% of eyes exhibited an IOP greater than 50 mm Hg at 40s post-surgery. Figure 1 illustrates the variations in IOP following intravitreal injection among the groups. A significant difference was observed in IOP at 5min among the seven groups ($F=2.50$, $P=0.029$), whereas IOP measurements at other time points did not significant differ ($P>0.05$).

Comparison of IOP Between Different Drug Groups Following Injections Subjects were categorized into three groups based on the type of drug used for intravitreal injections: IVO, IVC and IVR groups. The IOP values at various times before and after surgery were compared across these groups (Figure 2A). There were no significant differences in age, gender and baseline IOP among the three groups (t_1=0.02, χ^2=0.89, F_2=1.90, P>0.05). The average IOP 40s post-surgery was 14.43±6.68, 47.00±8.00 mm Hg, and 49.11±10.12 mm Hg for IVO, IVC, and IVR groups, respectively. The IOP in the IVO group was significantly lower at 40s after surgery compared to the IVC and IVR groups (F=37.65, P<0.001; Figure 2B). At 5min post-surgery, the IOP values was 18.32±5.40 mm Hg, 26.04±5.44 mm Hg, and 27.16±6.79 mm Hg, with the IVC and IVR groups showing significantly higher IOP compared to the IVO group (F=5.28, P=0.007; Figure 2C). However, no statistically statistically significant differences in IOP were observed between the IVC and IVR groups at any measured time point (P>0.05). Additionally, IOP differences at 15min, 30min, 60min, and 1d post-surgery among the three groups were not statistically significant (P>0.05).

Comparison of IOP Between Different Indication Groups Following Injections After excluding the IVO group, the remaining 75 eyes were classified according to indication into BVOME, CVOME, and non-RVOME groups. We compared the IOPs of the BVOME and CVOME with the non-RVOME groups at various time points pre- or post-surgery, as illustrated in Figure 3A and 3D). No significances were observed in age, gender, and IOP levels between the BVOME and CVOME groups pre- and post-surgery (P>0.05).

No significant differences in age, gender and baseline IOP were found between the BVOME and non-RVOME groups (t_1=0.33, χ^2=0.80, t_2=1.50, P>0.05). However, the BVOME group exhibited a significantly higher IOP at 40s post-injection compared to the non-RVOME group (t=5.16, P<0.001), with average IOP values of 57.85±5.60 and 44.92±7.77 mm Hg, respectively as shown in Figure 3B. Similarly, at 5min post-injection, the BVOME group had significantly higher average IOP values than the non-RVOME group (33.43±3.37 mm Hg *vs* 24.65±5.59 mm Hg; t=5.02, P<0.001) detailed in Figure 3C. No significant differences in IOP were observed at 15min, 30min, 60min and 1d post-injection between the groups (P>0.05).

Likewise, the CVOME group and the non-RVOME group showed no significant differences in age, gender, and baseline IOP (t_1=1.14, χ^2<0.01, t_2=0.42, P>0.05). However, the IOP at 40s was significantly higher in the CVOME group compared to the non-RVOME group (t=4.80, P<0.001; Figure 3E), with average IOP values of 58.78±5.50 and 44.92±7.77 mm Hg, respectively. At 5min, the CVOME group also demonstrated significantly higher average IOP values than the non-RVOME group, 32.30±4.58 *vs* 24.65±5.59 mm Hg (t=3.69, P<0.001) (Figure 3F). Similar to the BVOME comparison, there were no significant IOP difference at 15min, 30min, 60min and 1d post-injection (P>0.05).

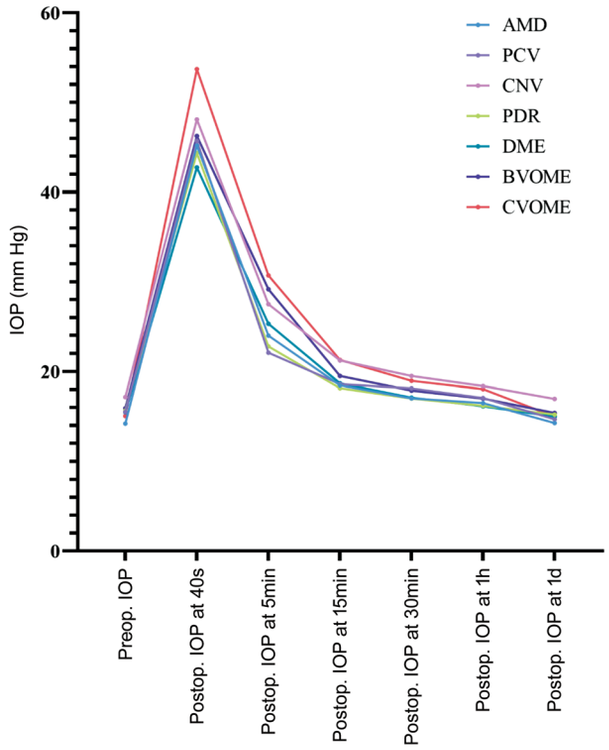

Figure 1 Fluctuation in IOP at different time points based on indications IOP: Intraocular pressure; AMD: Age-related macular degeneration; PCV: Polypoidal choroidal vasculopathy; CNV: Choroidal neovascularization; PDR: Proliferative diabetic retinopathy; DME: Diabetic macular edema; BVOME: Branch retinal vein occlusion macular edema; CVOME: Central retinal vein occlusion macular edema.

Comparison of IOP in Subject Stratified by Age and Gender After removing the IVO group, the remaining 75 eyes were categorized based on age (≤60 and >60y) and gender (male or female). The baseline IOP and IOP measurements at 40s, 5min, 15min, 30min, 60min, and 1d were compared between the two groups. No significant differences were observed in any of the comparisons (P>0.05; Figure 4).

Multivariate Logistic Regression Analysis To assess the IOP difference at various time points between the BVOME, CVOME and non-RVOME groups, after excluding the IVO group, a multivariate logistic regression analysis was conducted. This analysis considered age, gender, pre-operative baseline IOP, and postoperative IOP at 40s, 5min, 15min, 30min, 1h and 1d as independent variables. There were no statistically significant differences between the BVOME and the non-RVOME groups (Figure 5A). However, the CVOME group exhibited a significantly higher postoperative IOP at

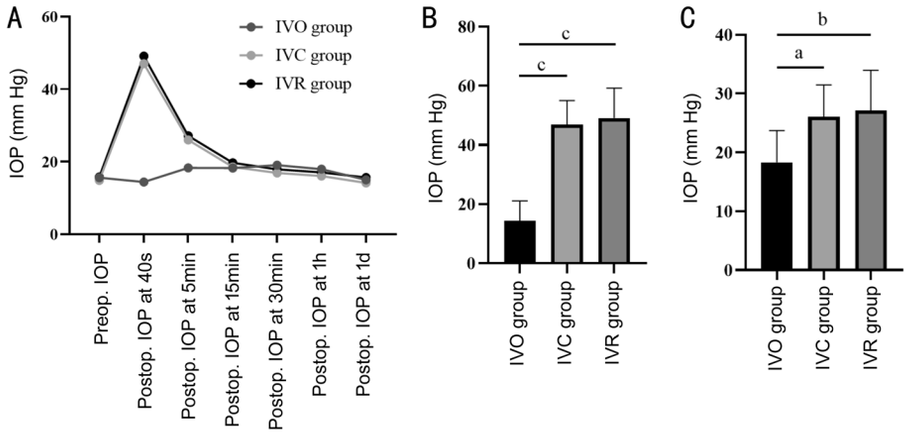

Figure 2 Comparisons of IOP at different time points among the IVO group, IVC group, and IVR group A: Pre- and post-operative IOP fluctuation curves of the three groups; B: Comparison of postoperative IOP at 40s (mean±SD) cross the three groups; C: Comparison of post-operative IOP at 5min (mean±SD) cross the three groups. IOP: Intraocular pressure; IVO: Dexamethasone intravitreal implant; IVC: Intravitreal conbercept; IVR: Intravitreal ranibizumab; SD: Standard deviation. [a]*P*<0.05, [b]*P*<0.01, [c]*P*<0.001.

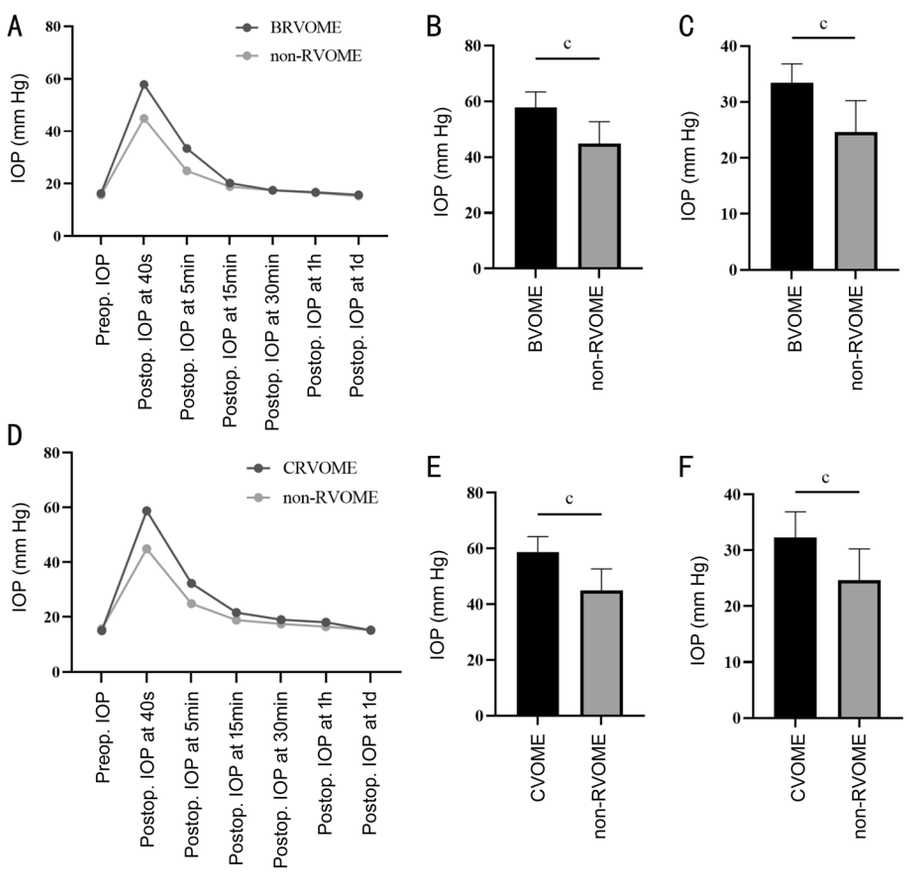

Figure 3 Comparisons of IOP at different time points between the RVOME and non-RVOME groups A-C: Comparison of IOP (mean±SD) between the BVOME group and non-RVOME group; D-F: Comparison of IOP (mean±SD) between the CVOME group and non-RVOME group. IOP: Intraocular pressure; BVOME: Branch retinal vein occlusion macular edema; CVOME: Central retinal vein occlusion macular edema; SD: Standard deviation. [a]*P*<0.05, [b]*P*<0.01, [c]*P*<0.001.

40s compared to the non-RVOME group [odds ratio (OR)=1.64, 95%CI: 1.09-2.47; *P*=0.018; Figure 5B].

DISCUSSION

Current evidence indicates that intravitreal injection of anti-VEGF medications causes a temporary surge in IOP[5]. Despite this, there is a lack of guidelines or consensus on measures to mitigate the impact of these IOP spikes on optic nerve. Furthermore, given the risk of retinal ganglion cell damage due to elevated IOP following injection, it is essential to manage both transient and persistent IOP fluctuations post-injection carefully. This is particularly important for patients with concurrent retinal diseases and glaucoma.

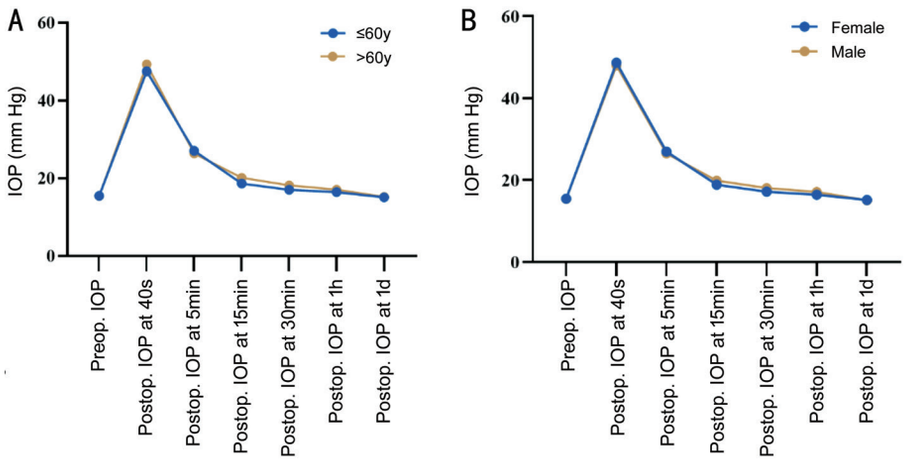

Figure 4 Fluctuation in IOP at different time points among different age (A) and gender (B) groups A: After removing the IVO group, IOP fluctuation curves were compared for different age (≤60 and >60y) groups; B: After removing the IVO group, IOP fluctuation curves were compared for different gender (male or female) groups. IOP: Intraocular pressure; IVO: Dexamethasone intravitreal implant.

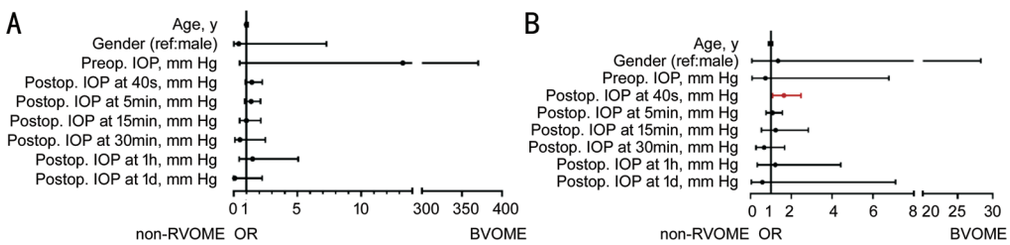

Figure 5 Multiple logistic regression analysis showed the comparisons of IOP at different time points after adjusting for age and gender A: Comparison between BVOME and non-RVOME groups; B: Comparison between CVOME and non-RVOME groups. IOP: Intraocular pressure; BVOME: Branch retinal vein occlusion macular edema; CVOME: Central retinal vein occlusion macular edema; OR: Odds ratio. $P<0.05$ indicates statistical significance.

In this study, choosen 40s as a time point post-injection, at which the earliset upright sitting position of the patient could be obtained to measure earliest IOP value after injection. The peak IOP across three groups occurred approximately 40s post-intraviteral injection, followed by a rapid decrease. The IOP then gently reduced at 15min and eventually stabilized by 30min. These findings align with prior research. Luqman *et al*[6] observed that IOP returned to a safe range within 30min post-bevacizumab intravitreal injection. Similarly, Kim *et al*[7] reported temporary IOP elevations after intravitreal injections of ranibizumab, bevacizumab, pegaptanib or triamcinolone acetonide, with IOP dropping below 30 mm Hg in 96% of the cases within 15min; however, eyes with a history of glaucoma showed a delayed normalization of IOP. In Arjmand *et al*'s[8] study, the comparison of post-injection IOP between ranibizumab, bevacizumab and pegaptanib revealed an IOP peak at 2min post-injection, suggesting that routine prophylactic use of IOP-lowering medications is largely ineffective in postoperative IOP management.

In this study, we observed higher IOP spikes at 40s and 5min post-injection in IVR and IVC groups (both treated with anti-VEGF drugs), and higher than that in IVO group at the two time points. These transient IOP elevations can be attributed to the temporary increase in vitreous cavity volumn post-surgery. The magnitude of postoperative IOP elevation, however, is influenced by various factors including needle size, vitreous cavity reflux volume, injection dosage, axial length, scleral thickness, and the initial volume of the vitreous cavity[9-10]. The scleral canal, often formed after needle withdrawal, leads to vitreous fluid reflux, with needle size positively correlating with reflux volume. However, this effect diminishes in patients with a larger initial vitreous cavity volume[11]. Notably, in our study, the needle diameter used in the IVO group (22G) was larger than those in the IVR and IVC groups (30G), likely contributing to greater reflux volume in the IVO group.

Our comparative analysis revealed that both the CVOME and BVOME groups exhibited higher IOP spikes at 40s and 5min post-injection compared to the non-RVOME group. After adjusting for confounders such as age, gender and preoperative baseline IOP, the IOP spike at 40s in the CVOME group was significantly higher than in the non-RVOME group, as per multiple regression analysis. Retinal vein occlusion (secondary macular edema), a prevalent retinal vascular disease treated with intravitreal anti-VEGF injections, has been a established association with glaucoma, is a key risk factor for increased post-injection IOP[12-14]. This increase is likely

due to obstructed aqueous humor outflow channels[15]. Venous occlusion or hypoperfusion is often accompanied by venous thrombosis which may due to the retinal vein stasis induced by higher IOP[12-13]. Furthermore, both central and branch vein thrombosis often occur simultaneously or late in glaucoma patients[16], which contributed to retinal vein stasis induced by higher IOP. Beaumont *et al*[17] observed that a larger cup-to-disc ratio (CDR) and higher IOP in RVO cases could indicate ischemia severity. Venous occlusion in the optic disc of the involved eye appears correlated with a larger CDR and higher IOP[14]. Notably, a retrospective study highlighted a signicantly higher incidence of primary angle-closure (PAC)/primary angle closure glaucoma (PACG) among RVO patients, with the highest frequency in central retinal vein occlusion (CVO) patients in comparison with hemicentral retinal vein occlusion (RVO) and branch retinal vein occlusion (BRVO) (11.5% *vs* 8.8% *vs* 3.1%), suggesting changes in the lamina cribrosa of the optic disc is a potential risk factor for CVO[18].

Our findings suggest that RVO eyes, especially those with CVO, exhibit higher peak IOP and slower recovery post-intravitreal injection. The occlusion in CVO often occurs in the lamina cribrosa or behind the optic nerve, whereas in BRVO, it is hypothesized to result from arterial pressure-induced thrombosis at arteriovenous intersections[19]. The more severe ciliary hyperemia in CVO, along with its higher correlation with the anterior iridal septum of the lens, may explain the higher IOP compared to BRVO. Current understanding points to a shared pathogenesis between ischemic CVO and glaucoma[20], though evidence remains scant for BRVO[21]. Moreover, inflammation, as indicated by elevated cytokine levels in the vitreous and aqueous humor in patients with CVO (compared with BRVO) plays a critical role in the pathophysiology, progression, and prognosis post-occlusion of CVO[14]. In summary above, we concluded that intravitreal injections of anti-VEGF result in higher IOP in CVO compared to other conditions. This disparity likely stems from several factors, including the site of vascular occlusion, the extent of ischemia, and the degree of inflammation.

The limitation of this study is that it is a case-control study with a limited sample size. The causal relationship or the exact mechanism between RVO and transit elevation of IOP is warranted by a large sample size and well-designed cohort study.

In conclusion, the significant short-term surge in IOP was observed in patients with RVO, particularly CVO, post-intravitreal injection warrants careful monitoring compared to other conditions. Considering this IOP trend (post-injection) in RVO (especially CVO) patients with a higher risk of primary glaucoma, comprehensive clinical assessments, such as gonioscopy before the surgery and followed by a tailored follow-up plan, is advisable. Although prevailing literature suggests primary glaucoma precedes RVO, our study found no glaucoma-related damage in RVO patients. Further research is needed to explore whether fluctuations in IOP post-injections independently contribute to RVO.

ACKNOWLEDGEMENTS

Authors' contributions: Miao JP: experimental design, data collection and collation, paper conception, article writing; Zeng YY: statistical analysis, mapping, literature search, article writing; Gu XM: statistical analysis, mapping; Zhang XY: experimental design, statistical analysis and research guidance, article writing.

Foundations: Supported by the National Natural Science Foundation of China (No.82070988); National Key Research and Development Program Intergovernmental Key Project (No.2024YFE0100900).

Conflicts of Interest: Miao JP, None; **Zeng YY,** None; **Gu XM,** None; **Zhang XY,** None.

REFERENCES

1 Avery RL, Bakri SJ, Blumenkranz MS, Brucker AJ, Cunningham ET Jr, D'Amico DJ, Dugel PU, Flynn HW Jr, Freund KB, Haller JA, Jumper JM, Liebmann JM, McCannel CA, Mieler WF, Ta CN, Williams GA. Intravitreal injection technique and monitoring: updated guidelines of an expert panel. *Retina* 2014;34(Suppl 12):S1-S18.

2 Zehden JA, Mortensen XM, Reddy A, Zhang AY. Systemic and ocular adverse events with intravitreal anti-VEGF therapy used in the treatment of diabetic retinopathy: a review. *Curr Diab Rep* 2022;22(10):525-536.

3 de Vries VA, Bassil FL, Ramdas WD. The effects of intravitreal injections on intraocular pressure and retinal nerve fiber layer: a systematic review and meta-analysis. *Sci Rep* 2020;10(1):13248.

4 Kontiola AI. A new induction-based impact method for measuring intraocular pressure. *Acta Ophthalmol Scand* 2000;78(2):142-145.

5 Levin AM, Chaya CJ, Kahook MY, Wirostko BM. Intraocular pressure elevation following intravitreal anti-VEGF injections: short- and long-term considerations. *J Glaucoma* 2021;30(12):1019-1026.

6 Luqman F, Bibi H, Mukhtar M, Zafar F, Ahmed H, Khizer MA, Gul N. Transient intraocular pressure fluctuations after intravitreal bevacizumab injection in proliferative diabetic retinopathy patients: a prospective study. *Cureus* 2023;15(9):e45371.

7 Kim JE, Mantravadi AV, Hur EY, Covert DJ. Short-term intraocular pressure changes immediately after intravitreal injections of anti-vascular endothelial growth factor agents. *Am J Ophthalmol* 2008; 146(6):930-934.e1.

8 Arjmand P, Yu CW, Popovic MM, Jhaveri A, Mandelcorn ED. Prophylactic intraocular pressure lowering measures in anti-vascular endothelial growth factor therapy: a systematic review and meta-analysis. *Surv Ophthalmol* 2023;68(3):425-445.

9 Garay-Aramburu G, Hunt A, Arruabarrena C, Mehta H, Invernizzi A, Gabrielle PH, Guillaumie T, Wolff B, Gillies MC, Zarranz-

Ventura J. Initial response and 12-month outcomes after commencing dexamethasone or vascular endothelial growth factor inhibitors for retinal vein occlusion in the FRB registry. *Sci Rep* 2024;14(1):6122.

10 Huang Y, Shao L, Yang J, Li P, Wei W. The necessity of early intraocular pressure measurement after intravitreal injection. *Chin J Ophthalmol Med (Electronic Edition)* 2021;11(6):353-358.

11 Kotliar K, Maier M, Bauer S, Feucht N, Lohmann C, Lanzl I. Effect of intravitreal injections and volume changes on intraocular pressure: clinical results and biomechanical model. *Acta Ophthalmol Scand* 2007;85(7):777-781.

12 Hayreh SS, Zimmerman MB, Beri M, Podhajsky P. Intraocular pressure abnormalities associated with central and hemicentral retinal vein occlusion. *Ophthalmology* 2004;111(1):133-141.

13 Klein BE, Meuer SM, Knudtson MD, Klein R. The relationship of optic disk cupping to retinal vein occlusion: the beaver dam eye study. *Am J Ophthalmol* 2006;141(5):859-862.

14 Jabbehdari S, Yazdanpanah G, Cantor LB, Hajrasouliha AR. A narrative review on the association of high intraocular pressure and glaucoma in patients with retinal vein occlusion. *Ann Transl Med* 2022;10(19):1072.

15 Bertelsen T. The relationship between thrombosis in the retinal veins and primary glaucoma. *Acta Ophthalmol* 1961;39:603-613.

16 Kim YJ, Sung KR, Lee KS, Joe SG, Lee JY, Kim JG, Yoon YH. Long-term effects of multiple intravitreal antivascular endothelial growth factor injections on intraocular pressure. *Am J Ophthalmol* 2014;157(6):1266-1271.e1.

17 Beaumont PE, Kang HK. Cup-to-disc ratio, intraocular pressure, and primary open-angle glaucoma in retinal venous occlusion. *Ophthalmology* 2002;109(2):282-286.

18 Xu K, Wu LL, Ma ZZ, Liu YL, Qian F. Primary angle closure and primary angle closure glaucoma in retinal vein occlusion. *Acta Ophthalmol* 2019;97(3):e364-e372.

19 Green WR, Chan CC, Hutchins GM, Terry JM. Central retinal vein occlusion: a prospective histopathologic study of 29 eyes in 28 cases. *Retina* 1981;1(1):27-55.

20 Kim YN, Shin JW, Park YJ, Lee JY, Kim JG, Yoon YH, Kim YJ. Glaucoma as a prognostic factor of central retinal vein occlusion: visual and anatomical outcomes and occurrence of ischaemic central retinal vein occlusion. *Acta Ophthalmol* 2021;99(4):e523-e530.

21 Han JC, Eo DR, Lee TK, Shin JH, Kee C. Does glaucoma share common pathogenesis with branch retinal vein occlusion? *PLoS One* 2016;11(6):e0156966.