Original Article

Effect of prophylactic intraocular pressure-lowering medication (brinzolamide) on intraocular pressure after ranibizumab intravitreal injection: A case–control study

Shuang Song, Xiao-bing Yu, Hong Dai

Purpose: To observe the effect of prophylactic intraocular pressure (IOP)-lowering medication (brinzolamide) on IOP after ranibizumab intravitreal injections (IVIs). **Materials and Methods:** This prospective case–control study included 352 eyes from 352 patients (1 eye per patient) who were treated with ranibizumab intravitreal injection and divided randomly into two groups. Two hundred and three patients in control group only received the ranibizumab IVI, but 149 patients in case group received one drop of prophylactic intraocular brinzolamide preinjection. The IOP was measured by noncontact tonometer before injection, at 10, 30, 120 min and 1 day after injection in a sitting position. **Results:** The mean IOP measured before injection, at 10, 30, 120 min and 1 day after injection individually were 15.79 ± 2.21 mmHg, 19.33 ± 4.86 mmHg, 16.64 ± 2.93 mmHg, 16.17 ± 3.13 mmHg, and 15.07 ± 2.55 mmHg in case group and were 15.82 ± 2.57 mmHg, 21.34 ± 5.88 mmHg, 18.17 ± 4.06 mmHg, 17.59 ± 4.42 mmHg, and15.48 ± 2.92 mmHg in control group. Comparing two groups, the mean increase on IOP was statistically significant at 10, 30, 120 min postinjection ($P < 0.05$). **Conclusions:** IVI of ranibizumab causes a considerable short-term transient rise on IOP in most patients. The effect of prophylactic IOP-lowering medication on IOP after IVIs can be statistically significant from 10 min to 2 h after IVIs.

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Intravitreal injection (IVI) therapy is getting more and more popular nowadays. Recently, the administration of anti-vascular endothelial growth factor (anti-VEGF) agents has become a new application of IVIs to treat a variety of retinal and choroidal neovascular diseases including neovascular age-related macular degeneration (AMD), central vein or branch vein occlusion with macular edema, and diabetic maculopathy.[1-4] Anti-VEGF drugs include the Food and Drug Administration-approved agent ranibizumab (Lucentis) which are VEGF-A inhibitors and the off-label use of bevacizumab (Avastin). Injection of ranibizumab into vitreous cavity obviously increases the intraocular volume by adding fluid, which can induce an increase in intraocular pressure (IOP) and can vary according to globe size, injected volume, scleral thickness, and scleral rigidity.[5,6] As the number of IVIs is growing, it is important to make sure these treatments are safe for patients. Up to now, many reports published that the injections may cause immediate or sustained IOP change.[7-12] Although these IOP elevation are common, it is unknown whether repeated IOP spikes may cause damage in predisposed eyes. Tsamparlakis noted that even transient IOP elevations can be associated with visual field defects[13] although sustained ocular hypertension can lead to significant optic nerve damage is well-known. Therefore, it may be necessary to control the IOP after IVI. Although both transient and sustained pressure rise after ranibizumab IVI are studied extensively in the Western population,[7-10] the conclusions about the effectiveness of IOP-lowering medications in preventing IOP increase after IVI from some studies are different. Theoulakis *et al*. reported that brimonidine/timolol-fixed combination may be effective to prevent the short-term IOP increase after IVI,[14] while Frenkel *et al*. suggested that routine prophylactic use of IOP-lowering medications is essentially ineffective in preventing IOP spikes after IVI.[15] Thereby, we investigated this prospective case–control study aiming to observe the effect of prophylactic IOP-lowering medication on IOP after ranibizumab IVIs.

Materials and Methods

Subjects

This prospective study followed the principles of the Declaration of Helsinki and was approved by the Hospital Ethical Committee, and all participants signed a standard informed consent form reporting the potential risks and benefits of the procedure and subsequent management. All patients were confirmed by the Ophthalmology Department of Beijing Hospital for a detailed examination including best-corrected visual acuity (BCVA) and IOP, slit-lamp biomicroscopy, auto refractometry, gonioscopy, and dilated fundoscopic examinations of both eyes.

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The study included 352 eyes from 352 patients (1 eye per patient) diagnosed exudative AMD, diabetic macular edema (DME), retinal vein occlusion (RVO), pathologic myopia (PM), idiopathic choroidal neovascularization (ICNV), or cystoid macular edema (CME) who were treated with ranibizumab (0.5 mg/0.05 ml) IVI between April 2013 and June 2014. Exclusion criteria included younger than 18 old years, ocular hypertension before injection, family history or a prior diagnosis of glaucoma, prior vitrectomy or phacoemulsification surgery, use of IOP-lowering agents, allergy to sulfur/sulphonamide-containing drugs. All the patients were divided randomly into two groups. In control group, 203 patients (mean ± standard deviation [SD], 64.21 ± 14.10 years) only received the ranibizumab IVI while in case group, 149 patients (mean ± SD, 61.54 ± 14.60 years) received one drop of prophylactic intraocular brinzolamide before ranibizumab IVI. The IOP was measured by noncontact Topcon tonometry (Japan) during the study.

For the operation procedure, injection of ranibizumab was performed at the upper pars plana with a sharp 30-gauge needle after complete sterile draping and rinsing with topical povidone-iodine under topical anesthesia with bupivacaine hydrochloride 0.75% eye drops. The injection site was located 3.5 mm posterior to the limbus. Both before and after IVI, patients were treated with levofloxacin eye drops for 3 days. No steroids eye drops were given. No eye received IOP-lowering medications or anterior chamber paracentesis before or after IVI. The IOP were measured before injection, at 10, 30, 120 min and 1 day after injection in a sitting position. One drop of brinzolamide was used after the baseline IOP measurement approximately 2 h (mean ± SD, 112.05 ± 26.61 min) before injection.

Statistical analysis

Statistical analysis was performed using SPSS (version 17.0) software (SPSS Inc., Chicago, IL, USA). Kolmogorov–Smirnov test of nonparametric analysis and Chi-square test were used to analyze the data of two groups. We set $P < 0.05$ (two-sided) with statistical significance in this study.

Results

Baseline characteristics

All patients completed each IOP measurement. The diagnoses of patients were as follows: Exudative AMD, DME, RVO, PM, ICNV, and CME. None of the study patients has significant intraoperative or shorter-term postoperative complications of operation or drugs such as endophthalmitis, hypersensitive to brinzolamide, or ranibizumab except high IOP. The baseline characteristics presented in Table 1 shows that the differences were not significant in gender, age, study eye, BCVA, and number of IVIs ($P > 0.05$) between two groups.

Table 1: Baseline characteristics

	Control group	Case group	*P*
Total patients	203	149	
Gender (%)			
Male	115 (56.65)	77 (51.68)	0.355†
Female	88 (43.35)	72 (48.32)	
Age (years)			
Mean±SD	64.21±14.10	61.54±14.60	0.102*
Eyes (%)			
OD	94 (46.31)	73 (48.99)	0.618†
OS	109 (53.69)	76 (51.01)	
BCVA (LogMAR)			
Mean±SD	0.75±0.49	0.78±0.47	0.825*
Number of IVIs			
Mean±SD	2.25±1.83	2.47±2.22	0.550*

*Two independent sample test, †Pearson Chi-square test. OD: Oculus dexter, OS: Oculus sinister, BCVA: Best-corrected visual acuity, IVIs: Intravitreal injections, SD: Standard deviation, LogMAR: Logarithm of the minimum angle of resolution

The changes of intraocular pressure after intravitreal injections

Outcome data collected included IOP measurements of baseline and immediately at 10, 30, 120 min and 1 day after IVIs. Table 2 individually shows mean IOP at baseline and after IVI of two groups. The mean IOP measured before injection, at 10, 30, 120 min and 1 day after injection individually were 15.79 ± 2.21 mmHg, 19.33 ± 4.86 mmHg, 16.64 ± 2.93 mmHg, 16.17 ± 3.13 mmHg, and 15.07 ± 2.55 mmHg in case group and were 15.82 ± 2.57 mmHg, 21.34 ± 5.88 mmHg, 18.17 ± 4.06 mmHg, 17.59 ± 4.42 mmHg, and 15.48 ± 2.92 mmHg in control group. The tendency in both curves is a sharp increase on IOP a few minutes after injection, with a gradual decline over the next hours. Maximum IOP elevation occurred at the time point of 10 min after injection in both groups. At time points of 10, 30, and 120 min postinjection, mean IOP was significantly higher in control group when compared with the case group ($P < 0.05$); however, the differences were not significant at baseline and after 1 day ($P = 0.463$). The mean postinjection IOP for control group at the time points of 10, 30, and 120 min was statistically different when compared with baseline IOP ($P < 0.05$). On the contrary, in case group, this difference was observed only for the time point of 10 min ($P < 0.05$).

Comparing two groups by Chi-square test, it indicated that the ratio of IOP ≥21 mmHg and the elevation of IOP ≥5 mmHg within 2 h after injection had significant difference as Tables 3 and 4 showed ($P < 0.05$).

Discussion

We found that the IOP increase after IVI in the control group of our study persisted for short period. Until 2 h after IVI, the IOP increase was statistically significant but no significance after 1 day. Similarly, Gismondi *et al*. reported that transient IOP increases within 30 min after IVI, however, there were no significant differences after half an hour.[7] Other published studies regarding IVI have reported transient IOP increases after 30–60 min, and stabilizing at baseline values after 1 day.[4,8,16] The little differences could be related to differences in the population race studied and/or IOP measurement techniques.

About the reasons of acute elevation of IOP after IVIs, the volume change of the vitreous cavity may be the main reason of immediate IOP increasing after ranibizumab IVIs. The volume of the vitreous cavity in human eye is 4 ml approximately, and the volume of ranibizumab injected into the vitreous is 0.05 ml. Therefore, the increase in fluid volume

Table 2: Mean intraocular pressure (mmHg) at before intravitreal and after intravitreal injection

Time	Case group		Control group		P†
	Mean±SD (range)	P*	Mean±SD (range)	P*	
Baseline	15.79±2.21 (11.0-20.3)	-	15.82±2.57 (9.5-20.7)	-	0.912
10 min after	19.33±4.86 (10.0-38.3)	0.000	21.34±5.88 (9.0-43.5)	0.000	0.004
30 min after	16.64±2.93 (9.0-26.0)	0.136	18.17±4.06 (8.5-36.0)	0.000	0.007
2 h after	16.17±3.13 (9.0-26.5)	0.287	17.59±4.42 (9.0-37.0)	0.000	0.030
1 day after	15.07±2.55 (9.0-22.3)	0.078	15.48±2.92 (9.0-24.7)	0.184	0.463

*Paired sample *t*-test, †Independent sample *t*-test. SD: Standard deviation

Table 3: Comparison of intraocular pressure ≥21 mmHg after injection

Time	IOP ≥21 mmHg				
	Case group (149)	Control group (203)	P	OR	95% CI
10 min after	52	102	0.004	0.531	0.344-0.820
30 min after	11	47	0.000	0.265	0.132-0.530
2 h after	9	43	0.000	0.239	0.113-0.508
1 d after	3	8	0.367	0.501	0.131-1.921

**P*<0.05. IOP: Intraocular pressure, OR: odds ratio, CI: Confidence interval

Table 4: Comparison of elevation of intraocular pressure ≥5 mmHg after injection

Time	Elevation of IOP ≥5 mmHg				
	Case group (149)	Control group (203)	P	OR	95% CI
10 min after	54	110	0.001	0.481	0.312-0.741
30 min after	6	38	0.000	0.182	0.075-0.443
2 h after	6	35	0.000	0.201	0.082-0.493
1 day after	1	3	0.640	0.450	0.046-4.374

**P*<0.05. IOP: Intraocular pressure, OR: odds ratio, CI: Confidence interval

of the vitreous cavity is 1.25% approximately, which may cause immediate IOP elevation. The block hypothesis for the potential mechanisms inducing an IOP elevation after IVI is that medications may block the immediate aqueous humor cycle channels, including the trabecular meshwork or Schlemm's canal outflow pathways by an unclear mechanism for several weeks or months.[10] Although these hypotheses are related to the sustained increased IOP, they may indicated that the ocular structure of patients with IVI have changed and are sensitive to the changes of the volume of the vitreous cavity. In addition, the daily fluctuation of the IOP may also play a role in the elevation of the IOP.

We also found that in case group of our study, patients use prophylactic IOP-lowering medication (brinzolamide) before injection have statistically significance only at 10 min after IVI. When comparing with the control group, the significant difference was observed up to 2 h. No matter the ratio of IOP ≥21 mmHg or elevation of IOP ≥5 mmHg, the results are similar within 2 h. Frenkel *et al*. reported that the IOP reduced to <30 mmHg in all patients within 20 min.[15] By contrast, Hariprasad *et al*. suggested that 13% of eyes with 30 mmHg or greater 30 min after injection.[17] However, they all indicated that prophylactic medication may not be necessary to prevent postinjection IOP spikes.[15,17] However, Theoulakis *et al*. reported that brimonidine/timolol-fixed combination may be effective to prevent the short-term IOP increase after IVI.[14] Kim *et al*. also indicated that the prophylactic administration of antiglaucomatic drugs before intravitreal anti-VEGF injection effectively reduced the early IOP elevation.[18] Similarly, in our study, under prophylactically using brinzolamide, the significant difference of IOP after injection between two groups is obvious within 2 h which may indicate that brinzolamide can successfully suspend the IOP rise. Considering the contrast to the previous studies, the time interval of using the prophylactic IOP-lowering medication before injection may an explanation. In this study, the time is approximately 2 h which is also the peak of IOP-lowering medication (brinzolamide) effectiveness; however, in Frenkel's study, the time interval was 5 min before injection which may be ineffective to decrease immediate IOP postoperation. Furthermore, another explanation as Kim *et al*. demonstrated that a lower IOP elevation with 27-gauge needles than with 30- or 32-gauge needles which may suggested that IOP rise may was more related to the needle diameter than to the volume injected.[19] Carnota-Méndez *et al*. supposed that a vitreous reflux occurs higher with a larger needle bore size which led to underestimate the probability of IOP rise.[20]

Giving topical pressure-lowering medications can reduce IOP, brinzolamide was used in this study to suppress the produce of aqueous humor mildly because of little side effects clinically comparing to other pressure-lowering medications. As is known that prostaglandin analogs are major pressure-lowering medications with great effect, but it is not

suitable for patients after IVIs. In addition, β blocker drugs have side effect for patients with some heart diseases.

Because the explanation of how high of ocular hypertension and how long high IOP lasting will damage the vision is unclear, we also cannot conclude that whether prophylactic IOP-lowering medication on IOP after ranibizumab IVIs is necessary. While as is known that patients should receive more injections to delay the loss of vision, every IOP rises even short may be harm to vision totally, especially for glaucoma or high IOP. IOP fluctuations in glaucoma or high-IOP patients, even at lower amplitudes, are a recognized risk factor for injury of optic nerve. Asrani *et al*. indicated that a diurnal variation of 5.4 mmHg in IOP was associated with a 5.7-fold increase in the progression of visual field loss.[21] Addition, Murray *et al*. suggested that prophylactic treatment may be considered as an option to minimize neuroretinal rim damage in high-risk glaucoma patients who are most vulnerable to IOP spikes and undergoing repeated IVIs of ranibizumab.[22] Therefore, this IOP elevation may be harmless in normal patients but should be taken into account on patients with ocular hypertension or glaucoma.

There are several limitations in our study. First, the most important limitation is that the noncontact tonometer is not golden standard tool like Goldmann tonometer though we had rectified it before measurement every time. Because we thought Goldmann tonometer may increase the risk of inflammation for the contact measure method and we focused on the changes of IOP and it may affect little relatively. Second, IOP elevation is much important to ocular hypertension or glaucoma patients; we did not investigate these patients which are another limitation of our study and we will make found research about this in further study. Third, the central corneal thickness and axial length as important factors for volume changes of ocular were not measured in this study, and the effect would be investigated in advanced study. In addition, this study just focused on short-term effect, but the long-term effect may affect optic nerve seriously which would be investigated in the further study. Although these limitations including population race, small sample size, ocular disease distribution, IOP measurement tool, unmeasured axial lengths, and operation procedure in this study may impact the result, we still insist that this study may help to illustrate the effect of prophylactic IOP-lowering medication on IOP after ranibizumab IVIs and whether the IOP-lowering therapy is necessary after IVIs. Therefore, further larger multiple centers studies are needed to make a definite conclusion.

Conclusions

IVI of ranibizumab causes a considerable short-term transient rise on IOP in most patients. The effect of prophylactic IOP-lowering medication (brinzolamide) on IOP after IVIs can be statistically significant from 10 min to 2 h after IVIs.

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Conflicts of interest

There are no conflicts of interest.

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