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The short-term effects of intravitreal bevacizumab injection on intraocular pressure, cornea, iridocorneal angle, and anterior chamber

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Abstract

Background: Transient increase in intraocular pressure (IOP), changes in anterior chamber parameters, and changes in aqueous humor dynamics may occur after intravitreal injections because of intravitreal volume changes.

Objective: In this observational study, we investigated the early effects of intravitreal bevacizumab (IVB) injection on IOP, central corneal thickness (CCT), corneal volume (CV), anterior chamber depth (ACD), and iridocorneal angle (ICA).

Method: The patients who had one single-dose IVB (2.5 mg/0.1 mL) injection were included in the study. The patients underwent IOP, CCT, CV, ACD, and ICA measurements before and 1 h and 1 day after the injection. Pre-injection and post-injection values were compared.

Results: Forty-two eyes of 42 patients were included in the study, and the mean age of patients was 60.1 ± 7.4 years. The mean IOP measurements before and after injection at 1 h and day 1 were 15 ± 2.4, 17.4 ± 2.4, and 14.7 ± 2.3, respectively. The mean IOP, CCT, and CV values 1 h after injection were significantly higher than pre-injection values ($p < 0.05$, $p < 0.05$, and $p = 0.02$, respectively). Conversely, mean ACD and ICA values 1 h after injection were significantly lower than pre-injection values ($p = 0.01$ for both). There were no statistically significant differences on the first day after injection for all parameters.

Conclusion: IVB (2.5 mg/0.1 mL) injection causes transient increases in IOP and transient decreases in ACD and ICA at the first hour after injection. Related to elevation in IOP, CCT and CV may increase transiently. These changes return to baseline values on the first day after injection.

Keywords: anterior chamber depth, bevacizumab, central corneal thickness, corneal volume, intraocular pressure

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Introduction

Bevacizumab, a recombinant monoclonal antibody, can bind to all forms of vascular endothelial growth factor (VEGF).[1] Although it is an approved treatment for colorectal cancer therapy, it has also been used in retinochoroidal disorders such as diabetic macular edema, age-related macular degeneration, choroidal neovascularization secondary to myopia, macular edema secondary to central retinal vein occlusion, and retinopathy of prematurity.[2–6] Intravitreal bevacizumab (IVB) injection may have ocular side effects such as subconjunctival hemorrhage, transient intraocular pressure (IOP) increase, vitreous hemorrhage, retinal detachment and endophthalmitis,[7,8] and systemic adverse effects such as sudden blood pressure elevation, venous thromboembolism, myocardial infarction, and stroke.[7,9]

After intravitreal injections, the intraocular volume increases by the amount of injected fluid.[10] Because of the acute intravitreal volume changes,

anterior chamber parameters and aqueous humor dynamics may be affected, and short-term IOP spikes may be seen.[10] Studies have also reported that bevacizumab may be detected in the aqueous humor after IVB injection.[11,12] Rabbit studies have shown that bevacizumab can be detected in the aqueous humor of both eyes for more than 1 month after intravitreal injection in one eye.[13] It has also been shown that the VEGF receptor is present in corneal endothelial cells.[14] Changes in corneal parameters after intravitreal injections may cause impaired visual quality, and changes in central corneal thickness (CCT) would affect IOP measurement. However, there is insufficient information in the literature about the effects of IVB on the human cornea and anterior chamber.

There are studies investigating the short and long-term effects of IVB on IOP elevation.[15–18] A study evaluating central corneal thickness (CCT) changes at day 1, day 7, month 3, and month 6 after IVB injection,[19] and a study evaluating CCT, anterior chamber depth (ACD) changes at day 3, day 15, and month 1 after IVB injection has been reported.[20] As far as we know, no study has evaluated the change in ACD, CCT, iridocorneal angle (ICA), and corneal volume (CV) at the first hour and first day after IVB injection. We wanted to evaluate the acute changes in IOP, corneal parameters, and anterior chamber parameters related to acute intravitreal volume increase 1 h after IVB (2.5 mg/0.1 mL) injection and whether these effects persist on the first day. Therefore, we aimed to provide additional information to the literature about the effects of IVB on corneal and anterior chamber parameters. In this study, we investigated the effect of IVB on CCT, CV, and ACD at the first hour and first day after IVB injection.

Materials and methods

This observational study was performed at the Gaziantep Dr. Ersin Arslan Training and Research Hospital between 20 July 2021 and 20 August 2021. The study was approved by Gaziantep Islamic Science and Technology University Ethics Committee. (Decision date: 13 July 2021, decision number: 41) The study was conducted following all the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant.

The patients who had one single-dose intravitreal bevacizumab injection were included in the study. Off-label use, potential risks, and benefits of the drug were explained to all patients before injection. Patients with anterior segment pathology, angle-closure, glaucoma, use of anti-glaucoma drugs, previous intraocular surgery (excluding phacoemulsification surgery) or laser therapy, and an axis length (AL) greater than 25 mm or less than 22 mm were excluded from the study. Routine ophthalmologic examinations, including best-corrected visual acuity measurements, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement via Goldmann Applanation Tonometry, and fundus examination were performed for all patients. In addition, pre-injection AL was measured by A-scan ultrasonography (Nidek US-4000 Echoscan, Nidek Co, Aichi, Japan).

ACD, CCT, ICA, and CV measurements were done using Sirius corneal topography and aberrometry system (Costruzione Strumenti Oftalmici, Italy) before IOP measurements. The corneal volume was measured in a diameter of 10 mm area. CCT, ACD, ICA, CV, and IOP measurements were performed before the injection and at the first hour and first day after the injection.

Intravitreal injections

The same surgeon (MB) applied a standard protocol for all intravitreal injections. First 0.5% proparacaine (Alcain, Alcon Covureur, Puurs, Belgium) was instilled for topical anesthesia, and then topical 5% povidone–iodine was instilled to sterilize the eyelids and the conjunctiva. The injection of bevacizumab (Avastin, Genetech Inc., San Francisco, California, USA; 2.5 mg/0.1 mL) was performed from the superotemporal quadrant 3.5–4 mm posterior to the limbus by using a 30-gauge needle. After the needle was removed, pressure was applied to the injection site to prevent vitreous leakage. Moxifloxacin 0.3% eye drops were given four times daily for 7 days.

The patients were examined, and the measurements were performed before injection and at the first hour and first day after the injection. The examinations and measurements were made by three experienced ophthalmology specialists (G.G., M.B., and C.O.).

Statistical analysis

All statistical analyses were performed using SPSS 20.0® for Windows (IBM Corporation,

Armonk, NY). The distribution of variables was measured with the Shapiro Wilk test. Analysis of variance (ANOVA) and Bonferroni correction were used to analyze the difference between pre-injection and two post-injection measurements. The value $p < 0.05$ was considered to be significant.

Results

Forty-two eyes of 42 patients [22 women (52.4%); 20 men (47.6%)] were included in this study. The mean age of patients was 60.1 ± 7.4 years (44–72 years). Thirty-one (73.8%) patients were pseudophakic, and 11 (26.2%) patients were phakic. The mean axial length of the eyes was 23.7 ± 0.7 mm (22.8–24.9 mm). The diagnoses of the patients are shown in Table 1. IOP, CTT, ACD, ICA, and CV measurements before injection and after injection at hour 1 and day 1 are shown in Table 2. None of our patients had a history of glaucoma, and none of them were using antiglaucomatous medication.

IOP measurements before injection and after injection at hour 1 and day 1 were 15 ± 2.4, 17.4 ± 2.4, and 14.7 ± 2.3, respectively. None of the patients had IOP above 30 mmHg at the first hour and the first day after injection. None of the eyes needed anterior chamber paracentesis. No patient was given topical antiglaucomatous drops following the injection.

At the first hour after the injection, IOP, CCT, and CV were significantly higher, and ICA and ACD were significantly lower than the pre-injection values. However, there were no statically significant differences at the first day after injection for all parameters (Table 2).

Table 1. Diagnoses of the patients.

Diagnosis	Number of patients
Diabetic macular edema	27
Age-related macular degeneration	8
Retinal vein branch occlusion	3
Central retinal vein occlusion	3

Discussion

The possible mechanisms of IOP increase after anti-VEGF injections may include acute volume increase related to the injected volume, damage to outflow due to the recurrent trauma, inflammation, and impaired outflow due to inflammatory debris.[21] The most likely cause of IOP increase after intravitreal injection is intravitreal volume increase, and it has been reported that higher intravitreal injection volume causes a more significant IOP change.[10] It has been mentioned that IVB might have a direct pharmacologic effect on the aqueous outflow and the cornea.[22–24] Also, theoretically, intravitreal fluid injection is expected to expand ocular tissues and change axial length and ACD.

An acute volume-related increase in IOP is the probable cause of IOP elevation after intraocular injections and may even cause short-term occlusion of the central retinal artery.[25] Cacciamani *et al.*[26] reported increased IOP at the first minute and 15th minute after IVB injection (1.25 mg/0.05 mL). Mazzulla *et al.*[16] reported a significant increase in IOP 30 min after injection of IVB (1.25 mg/0.05 mL) and a decrease in baseline IOP values 25 days after injection. Güler

Table 2. Comparison of the mean CTT, ACD, ICA, CV, and IOP measurements of the patients.

	Before injection	1 h after injection	24 h after injection
CCT (μm) (min–max)	534.46 ± 32.56 (468–596)	556.27 ± 44.18, $\mathbf{p < 0.05}$ (406–630)	535.48 ± 32.33, $p = 0.37$ (460–600)
ACD (mm) (min–max)	3.39 ± 0.48 (2.55–4.74)	3.29 ± 0.46, $\mathbf{p = 0.01}$ (2.44–4.17)	3.40 ± 0.51, $p = 0.89$ (2.57–4.78)
İCA (°) (min–max)	42.44 ± 8.26 (24–62)	39.95 ± 8.81, $\mathbf{p = 0.01}$ (26–62)	43.29 ± 8.13, $p = 0.61$ (25–60)
CV (mm^3) (min–max)	58.65 ± 3.26 (48.8–64.6)	60.52 ± 3.86, $\mathbf{p = 0.02}$ (51–67.3)	58.64 ± 2.95, $p = 0.97$ (51–64.4)
IOP (mmHg) (min–max)	14.98 ± 2.39 (10–21)	17.41 ± 2.39, $\mathbf{p < 0.05}$ (11–24)	14.70 ± 2.36, $p = 0.42$ (11–22)

ACD, anterior chamber depth; CCT, central corneal thickness; CV, corneal volume; ICA, iridocorneal angle; IOP, intraocular pressure; max, maximum; min, minimum.
$p < 0.05$ was considered to be significant.

et al.[20] evaluated the change of CCT, ACD, ICA, and IOP at the third, 15th day, and first month after IVB (2.5 mg/0.1 mL) injection and reported no significant difference. Alkin *et al.* evaluated the effects of IVB (1.25 mg/0.05 mL) on ACD and ICA at the fifth minute, first hour, and third hour after injection, and they have found a significant increase in IOP and a significant decrease in ICA and ACD at the fifth minute after injection. However, they reported no significant difference at the first hour and third hour after injection.[10] In addition, they reported a correlation between the decrease of ACD and elevation of IOP.[10] They also pointed out that the greater the injection volume, more increase in IOP and more decrease in the ICA and ACD.[10] They explained this by the fact that anterior displacement of the iris–lens diaphragm due to the injected volume may cause further reductions in ACD and ICA and a greater increase in IOP.[10] In our clinic, we use IVB at a dose of 2.5 mg/0.1 mL to provide a greater concentration in the vitreous and retina, and we evaluated the effects of IVB at this dose in this study. We found a significant increase in IOP and a significant decrease in ACD and ICA at the first hour after injection; however, these changes returned to baseline values on the first day after injections.

An increase in IOP is well known to cause corneal edema and an increase in CCT by affecting endothelial pump function.[27] Güzel *et al.*[28] found no significant difference in CCT after injection of three monthly doses of IVB (1.25 mg/0.05 mL). Similarly, Horozoglu *et al.*[29] reported no difference in CCT at the first week and the first month after injection of a single dose of IVB (1.25 mg/0.05 mL). Chiang *et al.*[19] applied IVB with the concentration of 2.5 mg/0.1 mL in their study, and they showed that the CCT did not change at the first and seventh day after IVB injection. We applied the same dose and found a significant increase in CCT and CV at the first hour after the injection; however, there was no significant difference on the first day after injection.

The inverse correlation between IOP and axial length after IVB injection has been reported.[26] Therefore, in our study, we included eyes with AL between 22 and 25 mm to avoid the differences in IOP change because of the wide range in AL. A more significant change in ACD was reported in pseudophakic eyes after injection of 0.1 mL of triamcinolone acetonide (TA) compared to phakic eyes.[30] This finding was explained by the possible relatively free movement of the intraocular lens in pseudophakic eyes after injection.[10,30] Approximately 75% of our patients were pseudophakic, and we observed a significant decrease in ACD at the first hour after injection. Kim *et al.*[17] showed that IOP was decreased to less than 30 mmHg in 96% of intravitreal injections by 15 min and 100% by 30 min. None of our patients had IOP more than 30 mmHg both 1 h and 1 day after injection.

The limitations of our study are small sample size, short follow-up period, focusing on very acute changes, absence of a control group, and absence of patients with glaucoma. In addition, we applied IVB at a dose of 2.5 mg/0.1 mL in our study which is larger than the commonly used volume in clinical practice, and unfortunately, there was not a comparison group that includes commonly used volume. Further studies with larger sample sizes and comparing different agents and injection doses are needed. In addition, studies investigating short-term IOP changes after intravitreal injections in eyes with glaucoma are needed.

In conclusion, the elevation of intravitreal volume after IVB injection with 2.5 mg/0.1 mL concentration causes an acute increase in IOP and an acute decrease in ACD and ICA. In addition, related to elevation in IOP, CCT, and CV may increase transiently. However, these changes return to baseline values on the first day.

Declarations

Ethics approval and consent to participate

The study was approved by Gaziantep Islamic Science and Technology University Ethics Committee on 13 July 2021. (Decision number: 41)

Consent for publication

Not applicable.

Author contributions

Gulsah Gumus: Conceptualization; Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

Mustafa Berhuni: Investigation; Methodology; Project administration.

Cem Ozturkmen: Project administration; Supervision; Visualization.

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