

# Effect of dorzolamide–timolol fixed combination prophylaxis on intraocular pressure spikes after intravitreal bevacizumab injection

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## Abstract

• **AIM:** To evaluate the effect of topical dorzolamide–timolol fixed combination prophylaxis on short term intraocular pressure (IOP) changes in patients who had intravitreal bevacizumab injection.

• **METHODS:** One hundred and fifty one eyes of 151 patients which were followed up in retina clinic in Ulucanlar Eye Training and Research Hospital were evaluated in this study. Patients were divided into two groups. Group 1 consists of 75 patients who had topical dorzolamid–timolol medication two hours before injection; while Group 2 consists of 76 patients without prophylaxis. Demographic data, IOP measurements prior to the injection and one, thirty and sixty minutes and twenty–four hours after the injection were recorded. The data were analyzed using SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA).

• **RESULTS:** There were no significant difference between two groups in age, gender distribution and indications for injections. The mean IOPs in Groups 1 and 2 prior to the injection ( $T_0$ ) were  $17.84 \pm 0.43$  and  $18.15 \pm 0.43$  mm Hg, one minute after the injection ( $T_1$ ) were  $29.75 \pm 1.6$  and  $34.44 \pm 1.59$  mm Hg, 30 minutes after the injection ( $T_{30}$ ) were  $20.06 \pm 0.6$  and  $21.71 \pm 0.59$  mm Hg respectively. The mean IOPs were  $18.26 \pm 0.56$  mm Hg in Group 1 and  $19.78 \pm 0.56$  mm Hg in Group 2 sixty minutes after the injection ( $T_{60}$ ). All IOP values after the injection were compared between two groups, there was a significant difference between two groups only on  $T_1$ ; one minute after the injection ( $P=0.04$ ). There were a statistically

significant difference between the baseline values and other recorded values; except on  $T_{60}$ , in Groups 1 and 2 ( $P < 0.05$ ).

• **CONCLUSION:** After intravitreal bevacizumab injection; we observe a transient IOP elevation which normalizes about one hour after intravitreal injection. In patients who had topical dorzolamid–timolol combination prophylaxis before injections, a significant decrease is seen in IOP spikes due to this injection. The appropriate approach will monitor IOP after intravitreal injection and evaluate the using prophylactic antiglaucomatous drugs before the injection in patients with ganglion nerve cell damage.

• **KEYWORDS:** bevacizumab; dorzolamid-timolol combination; intraocular pressure

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## INTRODUCTION

Intravitreal injections are common in ophthalmology practice and injection numbers are rapidly growing up with new indications. In 2020, the number of injections will reach about 40 millions according to a recent paper<sup>[1]</sup>.

Subconjunctival hemorrhage, corneal edema, conjunctival scar, retinal tears and detachment, lens damage and cataract development, choroidal rupture, vitreous hemorrhage, ocular hypertension and even endophthalmitis are complications of the intravitreal injections<sup>[2,3]</sup>. Intraocular pressure (IOP) elevation and glaucoma are frequently seen among these complications. IOP elevation may develop due to the injected volume in acute period after intravitreal injection, as well as sustained ocular hypertension may develop due to the pharmaceutical properties of the injected drug, total injection numbers and injection intervals<sup>[4-8]</sup>. After intravitreal triamcinolone acetate injections, 40% of the patients were diagnosed with ocular hypertension two to three weeks after the injection<sup>[9]</sup>. The steroid-induced structural changes in trabecular meshwork and resistance to the aqueous outflow may play a role in the development of steroid-induced ocular hypertension<sup>[10]</sup>.

On the other hand, the acute rises in IOP are usually transient but elevation may be a few to 80 mm Hg levels<sup>[5,11,12]</sup>. In patients with optic nerve damage, especially glaucoma, even a transient rise can cause ganglion cell damage. Animal models showed that an acute rise in IOP inhibits axonal transport and the damage will be significant with high IOP levels<sup>[13]</sup>. Therefore preventing the spikes is a conspicuous and important matter for ophthalmologists, there has been several studies. Many studies reported prophylactic anterior chamber paracentesis and Honan balloon compression after injections would be effective at preventing the IOP spikes<sup>[14-17]</sup>. Prophylactic antiglaucomatous medication may be another option to prevent the spikes. It is not clear which drug is most effective, moreover, there is no consensus about routine prophylactic treatment. Considering the fact that the use of anti-vascular endothelial growth factor (VEGF) drugs such as ranibizumab, bevacizumab are common worldwide, IOP spikes will become an important topic for clinicians<sup>[18,19]</sup>. There has been a few multicenter and comprehensive clinical studies about bevacizumab comparing to ranibizumab which has Food and Drug Administration (FDA) approval. Owing to cost effectiveness, bevacizumab is usually used as off-label treatment, as a result clinical studies may be limited.

In this study we evaluated the effect of topical dorzolamide-timolol fixed combination prophylaxis on short term IOP changes in patients who had intravitreal bevacizumab injections.

### SUBJECTS AND METHODS

Charts of patients which had intravitreal 0.05 mL (1.25 mg) bevacizumab injections from December 2012 to March 2013 retrospectively reviewed. Before performing bevacizumab injection, an informed consent were obtained, patients were informed about efficacy, complications and off-label use of the bevacizumab. The study protocol was complied with the provisions of the Declaration of Helsinki and permission was obtained from Diskapi Training and Research Hospital Ethics Committee.

The patients underwent complete ophthalmic examination including best corrected visual acuity, biomicroscopic anterior segment and fundoscopic evaluation, fundus fluorescein angiography (Kowa VX 10i, Kowa Optimed Co. Ltd., Tokyo, Japan) and optic coherence tomography (Spectralis, Heidelberg Engineering, Germany). Patients with vitreoretinal surgery history, posterior capsule rupture, ocular hypertension, glaucoma, active intraocular inflammation findings, ocular pathologies like pterygium and corneal opacities which will effect having reliable values were excluded in the study.

Demographic data, ophthalmologic examination findings, indications of the injections and IOP values prior to the injection ( $T_0$ ), on first minute after the injection ( $T_1$ ), thirty minutes after the injection ( $T_{30}$ ), one hour ( $T_{60}$ ) and one day

( $T_{24h}$ ) after the injection were recorded. The IOPs were measured using the TonoPen AVIA® (Reichert Technologies, NY, USA) applanation device, calibrated daily before the injections.

Patients were divided into two groups. Group 1 consists of 75 patients who had prophylactic dorzolamide-timolol fixed combination two hours before the injection and Group 2 (control group) consists of 76 patients who did not have prophylaxis before the injection.

All of the injections were performed in operating rooms. Bevacizumab flacons were kepted at appropriate storage conditions, and flacons were sealed just before the injections. Injections were performed with 27-gauge needles and massage were applied to the injection site to minimize the vitreous reflux. The central retinal artery perfusion and vision were checked with hand movements and patients were followed until IOP levels are normal. Topical antibiotics were prescribed and patients were discharged.

The collected data recorded and statistical tests were performed using SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA). Significance was accepted at  $P < 0.05$ .

### RESULTS

A total of 151 patients were included in this study. Group 1 consists of 48 (64%) female and 27 (36%) male patients while Group 2 consists of 40 (52.6%) female and 36 (47.4%) male patients. The mean age was  $64.6 \pm 10.1$  and  $62.6 \pm 10.9$  years old in Groups 1 and 2 respectively. There was no significant difference between two groups in age and gender ( $P = 0.26$ ,  $P = 0.16$  respectively).

There were 51 (68%) phakic and 24 (32%) pseudophakic patients in Group 1; and 59 (77.6%) patients were phakic and 17 (22.4%) patients were pseudophakic in Group 2. There was no significant difference between the groups in lens status ( $P = 0.18$ ).

The indications for injections were diabetic retinopathy [diabetic macular edema (DME) and proliferative retinopathy (PR)], retinal vein occlusion, neovascular age-related macular degeneration (ARMD) and chronic central serous chorioretinopathy. There has been no significant difference between two groups in distribution of indications ( $P = 0.68$ ; Table 1).

The mean IOPs prior to the injection were  $17.84 \pm 0.43$  mm Hg in Group 1 and  $18.15 \pm 0.43$  mm Hg in Group 2. After the intravitreal injections the mean IOPs in Group 1 and 2 were  $29.76 \pm 1.60$  and  $34.44 \pm 1.60$  mm Hg at  $T_1$ ,  $20.06 \pm 0.60$  mm Hg and  $21.71 \pm 0.60$  mm Hg at  $T_{30}$ ,  $18.26 \pm 0.56$  and  $19.78 \pm 0.56$  mm Hg at  $T_{60}$ ,  $13.84 \pm 0.41$  and  $14.06 \pm 0.40$  mm Hg at  $T_{24h}$  respectively. There were no significant difference between Groups 1 and 2 in IOP values at  $T_0$ ,  $T_{30}$ ,  $T_{60}$  and  $T_{24h}$  ( $P = 0.61$ ,  $P = 0.05$ ,  $P = 0.06$ ,  $P = 0.71$  respectively). But there was significant difference in IOP values at  $T_1$  between the groups ( $P = 0.04$ ; Table 2). The mean IOP elevation due to the the injection on first minute

**Table 1 Indications for intravitreal bevacizumab injections**

Indication	Group 1	Group 2	Total
Diabetic retinopathy (DME+PR)	49	47	96
Retinal vein occlusion	17	15	32
Neovascular ARMD	7	9	16
SSR	2	5	7
Total	75	76	151

DME: Diabetic macular edema; PR: Proliferative retinopathy; ARMD: Age-related macular degeneration; SSR: Santral serous retinopathy.

**Table 2 Mean intraocular pressures and comparison between groups**

Time	Mean IOP (mm Hg)		P Group 1 vs Group 2
	Group 1	Group 2	
T <sub>0</sub>	17.84±0.43	18.15±0.43	0.61
T <sub>1</sub>	29.76±1.60	34.44±1.60	0.04
T <sub>30</sub>	20.06±0.60	21.71±0.60	0.05
T <sub>60</sub>	18.26±0.56	19.78±0.56	0.06
T <sub>24h</sub>	13.84±0.41	14.06±0.40	0.71

IOP: Intraocular pressure; T<sub>0</sub>: Intraocular pressure prior to the injection; T<sub>1</sub>: First minute after the injection; T<sub>30</sub>: Thirty minutes after the injection; T<sub>60</sub>: One hour after the injection; T<sub>24h</sub>: One day after the injection. P is significant when <0.05.

was 11.91±14.32 mm Hg in Group 1 and 16.25±13.50 mm Hg in Group 2.

The highest IOP value was 54.95 mm Hg in five (3.31%) patients on T<sub>1</sub>. All patients had a visual acuity at least light perception level and all IOP spikes reduced spontaneously. Anterior chamber paracentesis or antiglaucomatous medication were not required in any patients to reduce IOP levels.

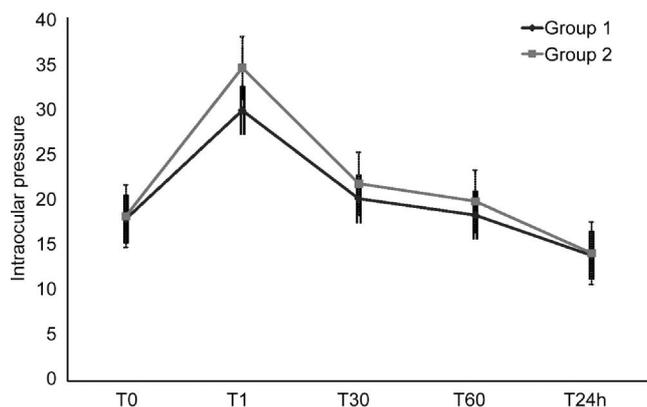
The IOP changes with time were similar between groups. There was a significant difference in IOP values between at T<sub>0</sub> and T<sub>1</sub>, T<sub>30</sub>, T<sub>24h</sub> in two groups (P<0.001). However in Groups 1 and 2, there was no significant difference between preinjection IOPs at T<sub>0</sub> and final IOPs at T<sub>60</sub> (P=1.00, P=0.06 respectively; Figure 1).

In pseudophakic and phakic patients, the IOP changes after intravitreal injections had a similar pattern with the time. There was no significant difference in IOP changes between pseudophakic and phakic patients in Group 2, while there a significant difference was determined in Group 1 (P=0.19, P=0.03 respectively; Figure 2).

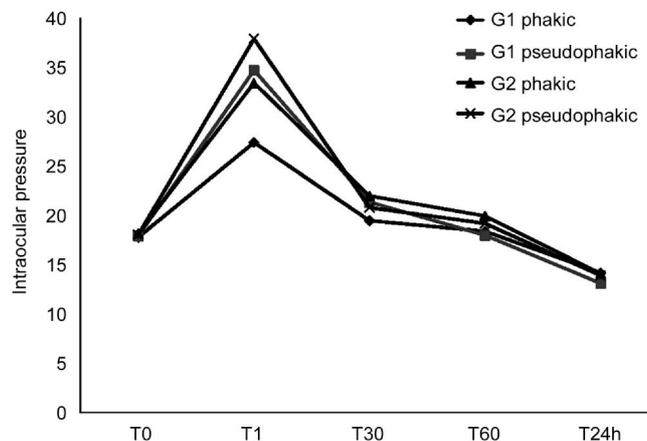
**DISCUSSION**

Intravitreal injection is a popular treatment modality for various vitreoretinal diseases. Total number of injections are growing up everyday, then it is important to evaluate the safety of the injections. The guideliness for intravitreal injections recommend monitorization of the IOP and surgical or medical intervention when the IOP elevation reaches risky levels<sup>[20]</sup>.

Many studies revealed an acute IOP elevation develops after intravitreal injections <sup>[5,9,21,22]</sup>. The elevations are mostly



**Figure 1 Intraocular pressure changes with time in Group 1 and 2 (bars represent the standart error of the mean) T<sub>0</sub>:** Intraocular pressure prior to the injection; T<sub>1</sub>: First minute after injection; T<sub>30</sub>: Thirty minutes after the injection; T<sub>60</sub>: One hour after the injection; T<sub>24h</sub>: One day after the injection.



**Figure 2 Intraocular pressure changes with time in pseudophakic and phakic patients T<sub>0</sub>:** Intraocular pressure prior to the injection; T<sub>1</sub>: First minute after injection; T<sub>30</sub>: Thirty minutes after the injection; T<sub>60</sub>: One hour after the injection; T<sub>24h</sub>: One day after the injection.

transient but its results are still suspicious, especially in patients with ganglion cell damage. As it is well known, IOP fluctuations in glaucoma is an independent risk factor for disease progression <sup>[23]</sup>. In a prospective study on the effect of diurnal variations in early glaucomatous damage, Gonzalez *et al*<sup>[24]</sup> found a positive correlation between IOP fluctuations and retinal nerve fiber layer defects.

Although IOP elevations are usually transient and depend on the injected volume, IOP may reach to levels that blocks the ocular perfussion pressure. Many cases reported that IOP reached at 87-89 mm Hg levels and anterior chamber paracentesis performed to reduce the IOPs <sup>[5,22]</sup>. Anterior chamber paracentesis would be a choice for preventing IOP spikes but contrary to the intravitreal injections, paracentesis takes longer time and the rate of complications like endophthalmitis, lens damage and cataract are frequent. And also timing of paracentesis is uncertain, whether before or after the injection. Knip *et al* <sup>[17]</sup> found prophylactic

anterior chamber paracentesis is effective at preventing IOP spikes, on the other hand, in a study Chang *et al*<sup>[16]</sup> reported routine anterior chamber paracentesis after the injections is inappropriate.

Because of the risk of complications and it's an invasive method, anterior chamber paracentesis wasn't accepted as a routine in practice and clinicians search for new treatment modalities to prevent the IOP spikes. Nowadays, studies on prophylactic antiglaucomatous medication before intravitreal injections are being popular and few studies reported their results<sup>[1,18,25]</sup>.

In this study we evaluated the short term IOP changes after intravitreal bevacizumab injection in patients with and without dorzolamide-timolol fixed combination prophylaxis. In our clinic, bevacizumab is used as off-label treatment for various vitreoretinal diseases frequently. Dorzolamide-timolol combination is effective than either dorzolamide and timolol and also the fixed combination reduces IOP more than conventional use. The fixed combination reduces IOP about 30%-35% and the time to peak effect is two hours after the application<sup>[26,27]</sup>.

Several drugs are used for prophylaxis in different application protocols. Kim *et al*<sup>[19]</sup> applied dorzolamide-timolol and brinzolamide-timolol fixed combinations one hour before the injection while El Cheab *et al*<sup>[1]</sup> applied the same drugs two hours before the injection in their study. Theoulakis *et al*<sup>[25]</sup> applied brinzolamide-timolol fixed combination for prophylaxis as twice a day the day before and the day of injection. It is not surprising that prostaglandin analogues was not an option for prophylaxis, as known they play a role in inflammatory process. In our study, the old patients' compliance with drugs and time to peak effect of drugs were considered; thus, dorzolamide-timolol fixed combination was chosen for prophylaxis and applied two hours before the injection.

Before the injection, there was no significant difference between the groups in IOP values. But first minute after the injection the difference were significant and the mean IOP was lower in the prophylaxis group. The mean IOPs and changes in IOP with the time reveals that there is a sudden elevation in IOP after the injection. The dorzolamide-timolol fixed combination prophylaxis cannot prevent the IOP spikes after the injection, nevertheless these elevations were mild with the prophylaxis. The high IOP levels normalised one hour after the injection in both groups. Similarly, Kim *et al*<sup>[19]</sup> reported IOP levels normalised in one hour in contrast to Theoulakis *et al*<sup>[25]</sup> and colleagues' study. They found IOP levels normalised 15min after the injection in prophylaxis group and 30min after the injection in control group. The difference in normalization curves may be developed due to their prophylaxis protocols was dense and taking two days as mentioned before.

Mean IOP were lowest at T<sub>24</sub> and a significant difference was found between IOP values only at T<sub>0</sub> and T<sub>24h</sub> in two groups. This difference was in both groups therefore it would not be an effect of the dorzolamide-timolol combination prophylaxis.

In pseudophakic and phakic patients the IOP changes were similar to each other. Kerimoglu *et al*<sup>[28]</sup> reported IOP values were normalized earlier in pseudophakic group than the phakic group after intravitreal injection. Gismondi *et al*<sup>[29]</sup> found any difference between phakic and pseudophakic patients on IOP changes by the time. In our study the changes in IOP was similar in phakic and pseudophakic patients although IOP levels were higher in the pseudophakic group. This result may be linked to the ratio of phakic and pseudophakic patients which are not equal in two study groups.

Information on short term IOP changes after intravitreal injections in patients with glaucoma is very limited. Kim *et al*<sup>[5]</sup> reported IOP normalized later in patients with glaucoma than without glaucoma after intravitreal injection while Frenkel *et al*<sup>[18]</sup> found similar normalization curves. For having reliable results, we excluded patients with glaucoma in the study groups. Total number of injections also were not considered in this study. Many studies revealed number of injections is a risk factor for sustained IOP elevations<sup>[7,30]</sup>. Short-term IOP changes are mostly developed by injected volume so that previous injections didn't considered in the study.

Most of the patients had intravitreal injections with the diagnosis of diabetic retinopathy (DME and PR). Second indication for injections was retinal vein occlusion and the third one was neovascular ARMD controversially to other studies<sup>[11,14]</sup>. Bevacizumab is cost effective than ranibizumab and has limited effects on IOP than triamcinolone acetate. These qualities made bevacizumab a good option for treatment in our country's social and economic conditions.

A portable tonometer, TonoPen AVIA was used for all measurements. TonoPen AVIA tends to overestimate IOP compared to Goldmann applanation tonometry at central corneal thickness greater than 520  $\mu\text{m}$  and underestimate IOP central corneal thickness at less than 510  $\mu\text{m}$ <sup>[31]</sup>. Repeated measurements, easy use in heavy working conditions, it is a good choice and have reliable results with daily calibrated before measurements. TonoPen AVIA has a range between 5 and 55 mm Hg. The highest IOP value was 54.95 mm Hg in our study. To be able to determine the values higher than 55 mm Hg, Goldmann applanation tonometer will be a good option for further studies.

With this study, we revealed IOP spikes after intravitreal injections and with dorzolamide-timolol fixed combination prophylaxis, these elevations may be mild. Like glaucoma, patients with optic nerve damage can be evaluated for prophylaxis before intravitreal injections and need close IOP monitoring after intravitreal injections.

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