ORIGINAL ARTICLE

Effect Of Prophylactic Use Of Fixed Combination Of Topical Dorzolamide And Timolol On Intraocular Pressure Spike After Intravitreal Bevacizumab

Ameera Jamil[1], Kanwal Zareen Abbasi[2], Maria Zubair[1], Seher Umer[1], Fuad Ahmad Khan Niazi[1]

Abstract:

Background: Intravitreal injections are common in ophthalmology practice and rapidly increasing with new indications. This study aims to identify the rise in the intraocular pressure following intravitreal Anti VEGF bevacizumab.

Objective: To evaluate mean changes in IOP among patients given intravitreal bevacizumab injection with topical dorzolamide and timolol fixed combination prophylaxis as compare to controls.

Methodology: It was a randomized control trial, conducted at ophthalmology department, Rawalpindi medical university and allied hospitals from March 2021 to December 2021. Patients were divided in two groups by lottery method. Group A was control group in which only intraocular pressure was measured before and after administration of intravitreal bevacizumab. While in Group B, cases given topical dorzolamide and timolol fixed combination prophylaxis before intravitreal anti VEGF bevacizumab were included. IOP in both groups was measured before and immediately after the procedure in supine position by hand held Perkin's tonometer. IOP was repeated immediately after injection, at 30 min and 60 min in both groups.

Results: Mean Intraocular pressure in Group-A before injection was 14.1+3.04 and in Group-B was 13.57+3.78 with p value 0.49. At 0 minute, it was 32.73+7.31 in Group A and 24.4+3.42 in Group B, p value was 0.0001. At 30 minutes, it was reduced to 22.57+5.38 in Group-A and 16.93+3.88 in Group-B, p value was 0.0001. At 60 minutes, IOP was 17.67+2.47 in Group-A and 14.9+3.30 in Group-B, p value was 0.001.

Conclusion: Mean changes in IOP in patients having intravitreal bevacizumab injection, with topical dorzolamide and timolol fixed combination prophylaxis, was significantly lower when compared to controls. *Al-Shifa Journal of Ophthalmology 2022; 18(4):162-171.*

1. *Rawalpindi Medical university*
2. *HBS medical and dental college, Ali Pur, Islamabad*

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Correspondence to:
Kanwal Zareen Abbasi
HBS medical and dental college, Ali Pur Islamabad
dr_maninoor_abbasi@yahoo.com

Introduction:

Intravitreal Anti vascular endothelial growth factors (Anti VEGFs) are widely used in different posterior segment diseases and injection numbers are rapidly increasing with new indications.[1]

Anti VEGF used in the treatment of vitreoretinal diseases are ranibizumab, aflibercept and bevacizumab. FDA approved anti vascular endothelial growth factors are ranibizumab and aflibercept for posterior segment diseases but bevacizumab is a widely used off label anti

VEGF and is cost effective and shows similar results.[1] Bevacizumab (Avastin) is used off label for various vitreoretinal diseases such as diabetic macular edema, choroidal neovascularization, proliferative diabetic retinopathy, retinopathy of prematurity and edema related to Central retinal vein occlusion.[1] There is an immediate rise in intraocular pressure after intravitreal anti VEGF agents [1,2]. The immediate rise in the intraocular pressure after intravitreal injection can cause blockage of the juxtapapillary retinal and optic nerve head axonal flow proportional to its quantitative rise and this can cause damage to retinal ganglion cell layer.[2.] Studies have shown that acute rise in the intraocular pressure blocks the axonal flow.[3] With these intravitreal injections; a transient IOP elevation occurs which normalizes about one hour after intravitreal injection.[4]Patients given prophylactic topical dorzolamide-timolol fixed combination get a significant decrease in IOP spikes during this 1st hour .[4] Similarly Brinzolamide was found to have IOP lowering effect when given prophylactically in patients who received intravitreal Ranibizumab.[5]

There are many international studies to find the effect of prophylactic use of fixed combination of topical dorzolamide and timolol on intraocular pressure spike after intravitreal bevacizumab, showing a significant decrease in IOP spikes. After literature review , we decided to conduct this study. Our study will help to find the effect of topical dorzolamide and timolol fixed combination prophylaxis on intraocular pressure spike after intravitreal bevacizumab injection in Pakistani population. As we hope that this measure will reduce the spike, so it will help to make the use of this prophylaxis mandatory so that marked post injection IOP rise can be prevented and so optic nerve blood flow cannot be compromised. This study was conducted to evaluate mean change in IOP in patients having intravitreal bevacizumab injection with topical dorzolamide and timolol fixed combination prophylaxis as compare to controls.

Materials and Methods:

This study was conducted in Benazir Bhutto Hospital, Rawalpindi medical university on patients having intravitreal bevacizumab injection for various indications, from 16-03-2021 to 31-12-2021. It was a randomized controlled trial. Patients were selected by non-probability convenient random sampling technique. Sample size was calculated by WHO calculator version 122.6 according to which 60 eyes were included in study. Patients were divided into two groups. Group A (Patients without prophylaxis, n=30), Group B (Patients who were given prophylactic topical dorzolamide-timolol combination n=30)

Patients included in study were those who were having any indication of intravitreal injection with age range 18 years to 80 years. Pseudophakic patients for less than 3 months, who underwent intravitreal injection of steroid less than 3 months, who underwent intravitreal antibiotic in less than 3 months and patients having glaucoma were excluded from study.

Before initiation of the study, approval was sought from the institutional ethics research forum of Rawalpindi Medical University. After an informed written consent from the patients, detailed history and ophthalmological examination were done for intravitreal injection and those fulfilling the criteria were included in study. Patients were divided in to two groups with lottery method. Group A was control group in which only intraocular pressure was measured before and after the administration of intravitreal bevacizumab and Group B were of cases whom topical dorzolamide and timolol fixed combination prophylaxis was given two hours before intravitreal bevacizumab.

Group A was control group, before procedure intraocular pressure was measured through hand held Perkin's

tonometer in the supine position on OT table and Group B was study group and include cases in which fixed combination of topical dorzolamide and timolol was instilled two hour before the procedure and Intraocular pressure was measured through hand held Perkin's tonometer pre-injection in the supine position on table.

After that, data collection procedure of both group was same. Patient was instilled with topical anesthesia Proparacaine, 5% povidone iodine was instilled into the conjunctival sac and around the eye lid. After scrub and drape under proper aseptic measures, eye speculum was applied. Eye was marked with the caliper 3.5mm from the limbus in pseudophakic and 4mm from the limbus in phakic eye in inferotemporal region. Injection bevacizumab of dose 1.25mg in 0.05ml was injected through pars-plana into the vitreous cavity and cotton bud was applied at the injection site for few seconds. At the end, 0.5% moxifloxacin was instilled in the conjunctival sac. After the procedure, immediately intraocular pressure was measured in supine position by hand held tonometer. It was repeated at 30 min and 60 min.

Statistical analysis was performed with SPSS version 20. Categorical variable such as gender, was expressed as frequency and percentage of patients and continuous variables such as age and intraocular pressure were expressed as mean +SD. Independent sample t test was used to make comparison between two groups and 'p' value less than 0.05 was considered as significant. Effect modifiers like age and gender was controlled by stratification. Post stratification independent sample t test was applied. P value <0.05 was considered as significant.

Results

A total of 60 cases (30 in each group) fulfilling the selection criteria were enrolled to evaluate mean change in IOP in patients having intravitreal bevacizumab injection with topical dorzolamide and timolol fixed combination prophylaxis as compared to controls.

Age distribution shows that 23.33% (n=7) in Group-A and 30%(n=9) in Group-B were between 18-50 years of age whereas 76.67%(n=23) in Group-A and 70%(n=21) in Group-B were between 51-80 years of age, mean age was 56.60+7.58 and 56.6+6.99 years respectively.

Gender distribution shows that 46.67%(n=14) in Group A and 36.67%(n=11) in Group B were male while 53.33%(n=16) in Group A and 63.33%(n=19) in Group-B were females.

Mean Intraocular pressure in Group-A was 14.1+3.04 and 13.57+3.78 in Group B, p value was 0.49. Mean IOP at 0 minute was 32.73+7.31 in Group A and 24.4+3.42 in group B, P value=0.0001.Mean IOP at 30 minute was 22.57+5.38 in Group-A and 16.93+3.88 in Group-B, p value was 0.0001, and Mean IOP at 60 minute was 17.67+2.47 in Group-A and 14.9+3.30 in Group-B , P value= 0.001. Results are shown in table 1,2 and 3.

Table-I: Stratification of Mean IOP at baseline and 0-minute post injection of both groups with respect to effect modifiers (gender, age,)

Variables	IOP time	Group A			Group B			P value
		Mean IOP	N	SD	Mean IOP	N	SD	
Males	Baseline IOP	12.21	14	1.76	11.91	11	1.92	0.68
	IOP at 0minute	30.71	14	8.14	25.45	11	2.84	0.05
Females	Baseline IOP	15.75	16	3.00	14.53	19	2.99	0.24
	IOP at 0minute	34.50	16	6.22	23.79	19	3.65	0.0001
Age 18-50 years	Baseline IOP	12.57	7	2.76	13.22	9	2.82	0.65
	IOP at 0minute	29.71	7	5.22	25.56	9	3.57	0.07
Age 51-80 years	Baseline IOP	14.57	23	3.03	13.71	21	3.00	0.36
	IOP at 0minute	33.65	23	7.69	23.90	21	3.32	0.0001

Table-II: Stratification of Mean IOP at baseline and 30-minute post injection of both groups with respect to effect modifiers (gender, age)

Variables	IOP time	Group A			Group B			P value
		Mean IOP	N	SD	Mean IOP	N	SD	
Males	Baseline IOP	12.21	14	1.76	11.91	11	1.92	0.68
	IOP at 30minute	21.93	14	4.27	17.36	11	2.62	0.004
Females	Baseline IOP	15.75	16	3.00	14.53	19	2.99	0.24
	IOP at 30minute	23.13	16	6.28	16.68	19	2.38	0.0002
Age 18-50 years	Baseline IOP	12.57	7	2.76	13.22	9	2.82	0.65
	IOP at 30minute	20.00	7	3.83	17.56	9	1.88	0.11
Age 51-80 years	Baseline IOP	14.57	23	3.03	13.71	21	3.00	0.36
	IOP at30minute	23.35	23	5.61	16.67	21	2.65	0.0001

Table-III : Stratification of Mean IOP at baseline and at 60-minute post injection of both groups with respect to effect modifiers (gender, age)

variables	IOP time	Group A			Group B			P value
		Mean IOP	N	SD	Mean IOP	N	SD	
Males	Baseline IOP	12.21	14	1.76	11.91	11	1.92	0.68
	IOP at 60minute	18.00	14	15.09	2.48	11	2.12	0.005
Females	Baseline IOP	15.75	16	3.00	14.53	19	2.99	0.24
	IOP at 60minute	17.38	16	2.50	14.79	19	1.93	0.001
Age 18-50 years	Baseline IOP	12.57	7	2.76	13.22	9	2.82	0.65
	IOP at 60minute	16.57	7	1.90	15.11	9	1.36	0.09
Age 51-80 years	Baseline IOP	14.57	23	3.03	13.71	21	3.00	0.36
	IOP at60minute	18.00	23	2.56	14.81	21	2.20	0.0001

Discussion

The intravitreal injections of anti-VEGF agents is now a common procedure performed by ophthalmologist for various vitreoretinal diseases such as diabetic macular edema , age related macular disease and choroidal neovascularization and other retinal pathologies. Anti VEGF agents include bevacizumab (Avastin; Genentech, Inc), ranibizumab (Lucentis; Genentech, Inc, South San Francisco, CA), pegaptanib (Macugen; Bausch & Lomb Inc., Rochester, NY), and aflibercept (Eylea; Regeneron, Tarrytown, NY) and they have provided significant benefit to patient with vitreoretinal diseases.[1,2,3]

There are many complications associated with Intravitreal anti VEGF injection in which Increase in IOP is a significant concern to ophthalmologist. Jong Wook Lee[2] in a prospective case series evaluated the Short-term changes of intraocular pressure and ocular perfusion pressure after intravitreal injection of bevacizumab or ranibizumab. Trial included 42 patients (65 eyes), who underwent intravitreal anti VEGF injection and IOP was measured just before the injection, immediately after the injection, at 30 min, 1 day, and 1 week after the injection. Their study showed that Pre-injection mean IOP was 16.66 ± 3.50 mmHg, and mean IOP was 43.81 ± 9.69 mmHg immediately after the injection. At 30-minute mean IOP was 17.57 ± 4.44. mean IOP at day 1 was 15.00 ± 4.21 mmHg, and mean IOP at week 1 was 15.90 ± 3.63 mmHg. IOP immediately after injection was significantly different from the pre-injection . In our study,we also observed the same transient increase in IOP elevation in the control group who receive intravitreal injection without prophylactic IOP lowering drops and 30 patients (30 eyes) were included in the control group A. Intraocular pressure in this group was 14.1$\pm$3.04, p value 0.49 before procedure and at 0 minute it was 32.73$\pm$7.31 and p value was 0.0001, which show that significant IOP spike occurred in the patients who received intravitreal Anti VEGF bevacizumab but this rise was quite less in group B who received prophylactic IOP lowering drops.

There are certain mechanism of actions suggested for the significant rise in the IOP after Anti VEGF injection. These include direct toxic effect of anti VEGF on trabecular meshwork, an inflammatory response to Anti VEGF, mechanical blockage of Trabecular meshwork by protein aggregates. Therefore, it remains an important clinical question about the relationship between Anti VEGF and Increase IOP after its use[3]. Timely recognition may postpone the onset or progression of Glaucoma and so prevents the visual loss.[3]

In many studies,[4,5,6] pre-treatment with topical dorzolamide and timolol fixed combination prophylaxis , brimonidine , acetazolamide , brimonidine or timolol and Anterior chamber tap before intravitreal injection have shown to help lower the IOP after Intravitreal anti VEGF. Anterior chamber tap is an invasive method and because of its risk of complications clinician have preferred to use topical prophylactic antiglaucoma medicine for clinical trial.[6]

Studies on prophylactic antiglaucoma medication before intravitreal injections are now being popular and few studies reported their results. Sehnaz Ozcaliskan[4] studied the effect of dorzolamide-timolol fixed combination prophylaxis on intraocular pressure spikes after intravitreal bevacizumab injection and evaluated the short term IOP changes after intravitreal bevacizumab injection in patients with and without dorzolamide-timolol fixed combination prophylaxis. They used Dorzolamide-timolol combination because of its effectiveness than either dorzolamide or timolol and because the fixed combination reduces IOP more than conventional use [4]. The dorzolamide-timolol fixed combination's effective peak time is 2 hours and it reduces IOP about 30%-35% after the application[6,7]. In our

study, we also used prophylactic dorzolamide and timolol fixed combination due to this advantage and we have also taken account of its availability in the hospital and its peak time effect of 2 hour which is convenient in our hospital setting and we have got the similar results.

Several drugs are used for prophylaxis in different protocols for reducing IOP after intravitreal anti VEGF. El Chehab [8] applied the brinzolamide-timolol and dorzolamide-timolol fixed combinations two hours before the injection in their study. Kim JN, et al [9] applied brinzolamide-timolol fixed combination for prophylaxis and noted that prophylactic administration of anti-glaucoma drugs prior to intravitreal anti-VEGF injection effectively reduced the initial intraocular pressure rise and concluded that his approach was also safe and could be performed accurately. Kim JE[10] applied brinzolamide-timolol and dorzolamide-timolol fixed combinations one hour before the injection. All of them found these prophylactic drugs effective as we found in our study.

Going into detail of Sehnaz Ozcaliskan's[4] study, the effect of dorzolamide-timolol fixed combination prophylaxis on intraocular pressure spikes, after intravitreal bevacizumab injection, was noted. In his study, patients were divided in to two groups. Group 1 consists of 75 patients who had topical dorzolamide-timolol medication two hours before injection and Group 2 consists of 76 patients without prophylaxis. Demographic data, IOP measurements was done prior to the injection and IOP was measured at one minute, 30-minute, 60 minute and 24 hours after the intravitreal avastin. He reported that there was no significant difference between two groups in age, gender distribution and indications for injections. The mean IOPs in Group 1 and Group 2 prior to the injection (T_0) were 17.84±0.43 and 18.15±0.43 mm Hg respectively, one minute after the injection (T_1) were 29.75±1.6 and 34.44±1.59 mm Hg, 30min after the injection (T_{30}) were 20.06±0.6 and 21.71±0.59 mm Hg respectively. The mean IOP was 18.26±0.56 mm Hg in Group 1 and 19.78±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).

In our study, there was no significant difference of age, gender distribution between two groups. Although, in our study intraocular pressure in Group-A was 14.1±3.04 and in Group-B was 13.57±3.78, p value was 0.49. At 0 minute, mean IOP was 32.73±7.31 in group A and 24.4±3.42 in group B, p value was 0.0001.At 30 minutes, it was reduced to 22.57±5.38 in Group-A and 16.93±3.88 in Group-B, p value was 0.0001, and at 60-minute mean IOP was 17.67±2.47 in Group-A and 14.9±3.30 in Group B, p value was 0.001.

Present study's results show that there is significant decrease in IOP elevation at O minute in group B who received prophylactic anti glaucoma topical dorzolamide and timolol fixed combination .Also there is significant difference between the mean IOP at 30 minute in both group. However, the difference in mean IOP at 60 minute in both group is 2.77mmhg which is insignificant.

Information on short term IOP changes after intravitreal injections in patients with glaucoma is very limited. Kim JE[10] reported IOP normalized later in patients with glaucoma than without glaucoma after intravitreal injection while Frenkel[8] found similar normalization curves. For having reliable results, we excluded patients with glaucoma in the study groups. Many studies revealed number of injections is a risk factor for sustained IOP elevations[5,11,12]. Short-term IOP changes are mostly developed by injected volume so that previous injections were not considered in

our study.
Sehnaz ozcaliskan[4] used a portable tonometer, TonoPen AVIA for the measurement of IOP. Tonopen was used for all measurements. In our study, we used Perkin's tonometer which is a portable tonometer and works on the same principle as Goldmann applanation Tonometer. It gives much more reliable IOP readings than tonopen and measures IOP greater than 55mmHg whereas tonopen measures between 5 and 55mmHg. Perkins tonometer was readily available in our hospital setting, easy to use and has reliable results.

Shoeib N, et al told that although it is advisable to prevent IOP spikes but use of prophylactic pressure-lowering medications with every mechanism of action has no effect in IOP spikes following intravitreal bevacizumab injections in non-glaucomatous eyes[13] which is against our study results. Two more studies revealed results contrary to our study. One is study of Farhood Q, et al, which shows that as IOP reverts back to safe range (25 mmHg) within 30 minutes after injection, so there is no need of any prophylactic topical medication [14] . 2nd is study of Mendez PC, et al who concluded that prophylactic topical IOP lowering medications are not helpful in reducing IOP when instilled 5 minutes before intravitreal bevacizumab injection[15] but on the other hand, results of Arjuman P et al's study again support our results where they checked the effect of prophylactic acute chamber paracentesis in some patients and topical pressure lowering medications in other patients and have concluded that these measures are quite effective in controlling the IOP rise after intravitreal Bevacizumab injection. [16]

Mirshahi A et al's study suggested that adjuvant topical timolol–dorzolamide in combination with IVB reduced post injection IOP spike and along with that also reduced the macular thickness in eyes with diabetic macular edema.[17]
Study of Chehab HE, et al showed the same results as ours showing that Intraocular pressure spike was high but transient and topical prophylactic medications were helpful in lowering the post injection spikes in glaucomatous as well as non glaucomatous eyes.[18]

Felfeli T et al used topical brimonidine tartrate prophylaxis for intravitreal injection of anti-VEGF agents and found it very effective in reducing the IOP spikes in non-glaucomatous eyes.[19] As studies confirm that eyes receiving first-time intravitreal bevacizumab injections show a significant increase in IOP within five minutes to two hours after intravitreal anti VEGF injections [20.] So, use of prophylactic topical IOP lowering medications was thought of a very good measure to reduce this pressure spike and this is what we have discussed in above of studies which supported the effectiveness of these topical medications.

All of above studies were about topical prophylaxis but Murray CD, et al. conducted a study where they used oral Acetazolamide 500mg 60-90 min before intravitreal injection and found the statistically significant effectiveness as of topical medications. They suggested the use of this prophylaxis to minimise neuro-retinal rim damage in high-risk glaucoma patients who are being given repeated intravitreal injections of ranibizumab.[21]

After analyzing the results of our study, we observed that there are IOP spikes after intravitreal injections and when given with dorzolamide-timolol fixed combination prophylaxis 2 hours prior to injection, these elevations were significantly reduced and this justified our hypothesis.

Conclusion

We observed that there is a transient IOP elevation in patients who receive intravitreal bevacizumab and prophylactic use of topical fixed combination dorzolamide and timolol 2 hour before procedure significantly reduces the IOP spike at 0 minute and 30 minute after

injection whereas at 60-minute difference is insignificant. The appropriate approach and more clinical trials will help to decrease the onset or progression of glaucoma in patient receiving intravitreal bevacizumab.

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Authors Contribution

Concept and Design: Ameera Jamil
Data Collection / Assembly: Seher Umer
Drafting: Maria Zubair
Statistical expertise: Ameera Jamil
Critical Revision: Kanwal Zareen Abbasi, Fuad Ahmad Khan Niazi