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ORIGINAL ARTICLE

Preventive effect of dorzolamide-timolol combination on intraocular pressure hikes after intravitreal bevacizumab (Avastin) injection.

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ABSTRACT… Objective: To evaluate the preventive effect of the dorzolamide-timolol fixed combination on intraocular pressure (IOP) spikes following intravitreal bevacizumab (Avastin) injection in patients with proliferative diabetic retinopathy (PDR). **Study Design:** Randomized Controlled Trial. **Setting:** Department of Ophthalmology, LRBT Tertiary Teaching Eye Hospital, Multan Road, Lahore. **Period:** July 2023 to December 2023. **Methods:** In this study we enrolled 60 cases equally divided in 2 groups: Group A (trial group) received prophylactic dorzolamide-timolol fixed combination eye drops 30 minutes before intravitreal bevacizumab injection, while Group B (control group) received no prophylaxis. Baseline IOP (T0) and post-injection IOP (T30) were measured using a Perkins applanation tonometer to know the mean IOP changes between groups. **Results:** There was a statistically significant difference in baseline IOP between the trial (9.08 ± 1.60 mmHg) and control (14.08 ± 2.00 mmHg) groups ($p < 0.001$). Post-injection IOP also remained significantly lower in the trial group (9.20 ± 1.60 mmHg) compared to the control group (15.37 ± 2.13 mmHg, $p < 0.001$). These findings indicate that prophylactic dorzolamide-timolol effectively prevents IOP elevation following intravitreal bevacizumab injection. **Conclusion:** Dorzolamide-timolol prophylaxis significantly reduces IOP spikes following intravitreal bevacizumab injection, highlighting its potential as a preventive strategy for patients at risk of ocular hypertension. Given the widespread use of anti-VEGF therapy, routine prophylactic IOP control may be beneficial, particularly for high-risk patients.

Key words: Bevacizumab, Dorzolamide-Timolol, Intraocular Pressure, Intravitreal Injection, Ocular Hypertension, Proliferative Diabetic Retinopathy.

INTRODUCTION

Intravitreal injection is now the gold standard for the treatment of most vascular diseases. Transient intraocular pressure (IOP) spikes are usual following intravitreal injections of anti-vascular endothelial growth factor drugs. There is no standard of care currently available to direct whether and when to prevent these IOP spikes. In addition, there are difficulties in ascertaining the effect of postinjection IOP increase on the retinal ganglion cell health, especially in light of frequently present comorbidities of glaucoma and retinal pathology. Anti-VEGF, antibiotic, and steroid intravitreal injections are the three types that are most frequently used.[1] The most prevalent disorders treated with intravitreal anti-VEGF medications are ARMD, retinal vein occlusion and proliferative diabetic retinopathy. Bevacizumab (avastin), 1.25 mg/0.05 ml, Ranibizumab (lucentis), 0.5 mg/0.05 ml, Aflibercept (Eylea), 2.0 mg/0.05 ml, and Brolucizumab (Beovu), 6.0 mg/0.05 ml, are the most widely used anti-VEGFs. All currently utilised intravitreal agents carry the risk of increasing IOP and Lenticular opacities after intravitreal injection.[2]

The range of the normal IOP is 12 to 20 mmHg. Patient's vision might be harmed by having pressure that is either too high or too low. IOP rise may result from the volume of drug administered in the immediate aftermath of intravitreal injection, and prolonged ocular hypertension may result from the drug's pharmacological characteristics, total number of injections, and injection intervals.[1-2]

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Among 104 patients, 85% were managed for neovascular age-related macular degeneration. Without prophylactic antiglaucoma therapy, mean IOP increased from 14.0 mmHg at baseline to 36.1 mmHg at 2 minutes, decreasing to 25.7 mmHg at 5 minutes and 15.5 mmHg at 30 minutes. Notably, 2.9% of patients (n=3) had an IOP of ≥25 mmHg at 30 minutes post-injection.[3-4] Intraocular pressure (IOP) can experience acute yet transient elevations, sometimes reaching as high as 80 mm Hg.[5-8] Even short-lived increases in pressure may pose a risk to ganglion cells, particularly in individuals with optic nerve damage, such as those with glaucoma. Consequently, several studies emphasize the importance of preventing these IOP spikes in clinical practice. Research has highlighted that interventions like Honan balloon compression and anterior chamber paracentesis are effective in reducing IOP following injections.[9-11]

Another study to mitigate sudden increases in IOP is the prophylactic use of anti-glaucoma medications. In a study involving 166 patients (175 eyes) scheduled for intravitreal anti-VEGF injections, some received pre-treatment with Dorzolamide/Timolol (Cosopt,® MSD) or Brinzolamide/Timolol (Elazop,® Alcon), while others remained untreated (Group 3, 29 eyes). Intraocular pressure was measured five minutes before the injection, then at five-minute intervals for 30 minutes post-procedure, followed by assessments at one hour, one day, seven days, and one month. The recorded IOP values at the time of the procedure, five minutes after the baseline measurement, were 12.06 ± 1.85 mmHg in Group 1, 13.98 ± 2.68 mmHg in Group 2, and 13.81 ± 2.24 mmHg in Group 3. A significant deviation from baseline was observed in all three groups at 5 and 30 minutes post-injection. With the increasing global use of anti-VEGF agents such as ranibizumab and bevacizumab, addressing IOP spikes remains a critical concern for ophthalmologists.[12-16]

METHODS

This randomized controlled trial was conducted at the Ophthalmology Department, LRBT, Lahore, over a period of six months from July 2023 to December 2023 after approval from ethical committee (CO/Admin/Doc-264)7/6/23). Intraocular pressure (IOP) was defined as the pressure within the treated eye of patients with PDR, measured in millimeters of mercury (mmHg) using a Perkins applanation tonometer. This instrument was calibrated daily before measurements to ensure accuracy. Bevacizumab (Avastin) is a lab-made antibody that blocks a protein called VEGF, which is responsible for forming new blood vessels, helping to slow abnormal blood vessel growth. In this study, patients received a standard dose of 1.25 mg/0.05 ml of Avastin, manufactured by Roche Pakistan Ltd. Proliferative diabetic retinopathy was identified as a chronic, progressive, sight-threatening disease of the retinal microvasculature, diagnosed based on the presence of neovascularization observed during posterior segment evaluation. The sample size was calculated as 60 cases(30 cases in each group) using an 80% power of the test, a 5% margin of error, and previously reported mean IOP values of 10.06 ± 1.85 mmHg in the dorzolamide-timolol group and 13.8 ± 2.24 mmHg in the control group. Non-probability consecutive sampling was used for patient selection.

Patients aged 35–65 years of both genders, who required repeat intravitreal bevacizumab injections and had a normal baseline IOP (≤ 21 mmHg), were included in the study. Only patients with confirmed PDR, identified by neovascularization on posterior segment evaluation, were eligible. Patients with a history of vitreoretinal surgery, ocular hypertension, posterior capsule rupture, glaucoma, or active intraocular inflammation were excluded. Additionally, patients with ocular pathologies such as pterygium or corneal opacities, which could interfere with accurate IOP measurement, were also excluded.

Before undergoing intravitreal injection, patients provided informed consent after receiving detailed information regarding the efficacy, potential adverse effects, and off-label status of bevacizumab. A thorough ophthalmologic examination was performed, including best corrected visual acuity (BCVA) assessment, biomicroscopic anterior segment evaluation,

and posterior segment evaluation with a 90D lens. Baseline intraocular pressure (T0) was measured 30 minutes prior to injection using a Perkins applanation tonometer. Patients were then randomly allocated into two groups through a lottery-based method. Patients in group A (trial group) received prophylactic dorzolamide-timolol fixed combination eye drops 30 minutes before the intravitreal injection, while patients in group B (control group) received no prophylactic treatment. All injections were performed under aseptic conditions in an operating room, using a 27-gauge needle. Following the injection, topical antibiotics were prescribed according to standard protocol. To know the difference between both techniques we compared IOP after 30 minutes of the procedure with the help of SPSS-23 (independent-t test).

RESULTS

A mean age of 51.9 years (±8.97). The age distribution showed that 41.7% (n=25) of the patients were between 35 and 50 years old, while 58.3% (n=35) were older than 50 years. Gender distribution was nearly equal, with 48.3% (n=29) males subjects and 51.7% (n=31) female subjects. Regarding laterality, the majority of patients (60%, n=36) had involvement in the right eye, while 40% (n=24) had the left eye affected. (Table-I)

The study further evaluated the preventive effect of the dorzolamide-timolol combination on intraocular pressure (IOP) fluctuations following intravitreal bevacizumab (Avastin) injection. At baseline, the mean IOP in the trial group (patients receiving dorzolamide-timolol) was 9.08 ± 1.60 mmHg, while in the control group, it was significantly higher at 14.08 ± 2.00 mmHg (p = 0.000). Post-injection, a similar trend was observed, with the trial group maintaining a stable IOP of 9.20 ± 1.60 mmHg, whereas the control group experienced a notable increase to 15.37 ± 2.13 mmHg.(p=<0.000). (Table-II)

These findings indicate that the dorzolamide-timolol combination effectively prevents IOP spikes following intravitreal bevacizumab injection. The trial group exhibited consistently lower IOP values both before and after the injection compared to the control group, highlighting the potential of this intervention in mitigating pressure fluctuations associated with the procedure.

Variable	Group	Count	Percent
Age	35-50	25	41.7
	>50	35	58.3
Gender	Male	29	48.3
	Female	31	51.7
Laterality	Right Eye	36	60.0
	Left Eye	24	40.0

Table-I. Demographics of the patients (n=60)

Variable	Group	IOP	P-Value
Baseline IOP	Trial Group	9.087+1.60	0.000
	Control Group	14.08+2.00	
Post Injection IOP	Trial Group	9.20+1.60	0.000
	Control Group	15.37+2.13	

Table-II. The preventive effect of dorzolamide- timolol combination on intraocular pressure hikes after intravitreal bevacizumab (Avastin) injection (N=60)

DISCUSSION

This study demonstrated that prophylactic treatment with a dorzolamide-timolol fixed combination significantly lowers IOP spikes after intravitreal bevacizumab (Avastin) injection in patients with PDR. The mean IOP in the trial group was markedly lower before and after the injection compared to the control group (P < 0.000). This indicates that dorzolamide-timolol effectively mitigates acute IOP elevations following intravitreal anti-VEGF injections, offering a promising preventive approach for managing IOP fluctuations.

Our results are aligned with previous data that have investigated the effect of prophylactic anti-glaucoma medications on IOP spikes after intravitreal anti-VEGF injections. Özçalışkan et al[17] reported that patients receiving dorzolamide-timolol two hours before intravitreal bevacizumab injections had significantly lower IOP one minute post-injection (p=0.04). Similarly, Kim et al[18] found that dorzolamide-timolol and brinzolamide-timolol significantly reduced early IOP elevations following anti-VEGF injections. Additionally, Pece & Allegrini[19] showed that timolol 0.1% gel,

when administered two hours before intravitreal ranibizumab injections, effectively reduced IOP spikes, particularly those exceeding 40 mmHg. These studies support the notion that prophylactic anti-glaucoma medication can prevent significant IOP elevations.

However, not all studies support these findings. Coşkun et al[20] evaluated the effect of dorzolamide-timolol before intravitreal ranibizumab injections and found no significant reduction in IOP changes post-injection. The discrepancy between our study and theirs could be attributed to differences in methodology, such as the use of different IOP measurement techniques, variations in patient selection, and differences in pharmacokinetics between bevacizumab and ranibizumab. Additionally, de Vries et al. conducted a systematic review and meta-analysis that concluded while intravitreal injections cause transient IOP elevations, IOP generally returns to baseline within 24 hours, suggesting that routine prophylactic treatment may not be necessary for all patients.

The clinical implications of our findings are significant. Given the increasing number of intravitreal anti-VEGF injections performed worldwide, IOP spikes remain a critical concern, particularly for patients with pre-existing glaucoma, optic nerve damage, or compromised retinal microcirculation. The prophylactic use of dorzolamide-timolol could help mitigate these pressure fluctuations, reducing the risk of optic nerve damage. This intervention is not only effective but also non-invasive, widely available, and cost-effective compared to other IOP-lowering measures, such as anterior chamber paracentesis. Furthermore, preventing extreme IOP spikes (>40 mmHg) may reduce the need for emergency interventions, thereby preserving the long-term health of the optic nerve.

While our findings are encouraging, we must acknowledge the study's limitations. The inclusion of only 60 patients may affect the applicability of our results to a larger population. Additionally, the short follow-up duration only assessed IOP changes within 30 minutes post-injection, whereas longer follow-up studies could provide more insight into the long-term impact of repeated IOP fluctuations. Another limitation is the use of a single measurement technique (Perkins applanation tonometer), which, although reliable, could be validated further using alternative tonometry methods. Furthermore, our study excluded patients with glaucoma, who are at the highest risk of IOP-related complications. Future research should specifically assess the impact of dorzolamide-timolol in this high-risk subgroup.

To build on these findings, future studies should explore the long-term effects of repeated IOP spikes, especially in patients receiving multiple anti-VEGF injections over time. Additionally, comparative studies evaluating the effectiveness of different prophylactic agents, such as brimonidine, acetazolamide, or apraclonidine, could help determine the most optimal approach for preventing IOP spikes. Personalized prophylactic strategies, based on individual patient risk factors, should also be explored to ensure that high-risk patients receive the most appropriate intervention.

CONCLUSION

We found that dorzolamide-timolol, when used prophylactically, effectively prevents IOP spikes after intravitreal bevacizumab injections in proliferative diabetic retinopathy patients. Given the significant risk of IOP elevation after anti-VEGF injections, prophylactic IOP control should be considered, particularly for high-risk patients. While our findings advocate for the use of dorzolamide-timolol, further investigations involving broader patient populations and prolonged observation periods are essential for establishing clear clinical recommendations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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1	**Hassam Mukhtar:** Data collection, paper writing.
2	**Zukhruf Ijaz:** Discussion writing, review of manuscript.
3	**Amna Iqbal:** Data collection, analysis, paper writing.
4	**Sidra Zafar:** Review of manuscript.
5	**Talha Nafees:** Literature review, data entry.
6	**Kashif Saleem:** Data analysis, review of manuscript.