Intraocular Pressure Changes After Intravitreal Injection of Bevacizumab In Patients With Diabetic Macular Edema

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ABSTRACT

Objective To find out the change in the mean intraocular pressure at various time intervals after *intravitreal injection of bevacizumabÊin patients with diabetic macular edema.*

Study design *Prospective cohort study.*

Place & Duration of study *The Layton Rahmatulla Benevolent Trust (LRBT) Tertiary Teaching Eye Hospital Korangi Karachi, from March 2023 to August 2023*

Methods *Intravitreal injection of bevacizumab (1.25mg) was administered via the pars plana region, 3.5-4.0 mm from the inferotemporal limbus. Intraocular pressure (IOP) was assessed immediately after injection. Patients were followed on day-1, one-week, and after one-month. The repeated measures of ANOVA test was used to compare the mean changes in IOP. A p value of <0.05 was taken as significant. Independent (student) t-test was applied for comparison of continuous variables (e.g., IOP, RNFL thickness, macular thickness) between two independent groups such as gender, age groups, and presence or absence of side effects*

Results *A total of 150 patients with 82 (54.7%) males and 68 (45.3%) females were enrolled. Seventy-eight (52%) patients were =45-years of age. Fourteen (9.3%) individuals exhibited a very mild condition, whereas 69 (46%) presented with a light condition. Moderate and severe condition were noted in 21 (14%) participants each, whereas 25 (16.7%) patients had a very severe condition. Adverse effects were reported by 49 (32.7%) patients.*

Immediately following the bevacizumab injection, the IOP was 24.23±3.98 mmHg. After 1-day, IOP was 20.67±4.03 mmHg, indicating a considerable reduction from immediate post-injection level. After one-week, IOP was 16.99±3.39 mmHg, and 16.44±3.37 mmHg after one-month.

Conclusion *The administration of intravitreal bevacizumab resulted in a temporary increase in intraocular pressure, that subsided within a day and then continued to decline over a period of one-month.*

Key words *Intraocular Pressure, Intravitreal injection, Bevacizumab, Diabetic macular edema, Vascular endothelial growth factor.*

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INTRODUCTION:

Diabetic macular edema (DME) is the primary cause of visual impairment in diabetic patients.[1] The genesis of DME is influenced by a number of factors.[2] The most common mechanism causing DME is the breakdown of the blood-retinal barrier (BRB) and increased vascular permeability, which causes fluid to accumulate inside the macula's intra-retinal layer One important factor that damages blood-retinal barrier and the starts the process of angiogenesis

is vascular endothelial growth factor (VEGF). In the past, focal photocoagulation was thought to be the most effective treatment for diabetic macular edema. However, after three-year follow-up, 12% of the eyes treated with lasers, lose 15 or more ETDRS letters. At 12-month follow-up, retinal thickening affecting the fovea was seen in around 40% of these treated eyes.[1]

A glycoprotein called vascular endothelial growth factor is necessary for a number of physiological processes like healing. However, it can cause irreversible loss of vision, including diabetic retinopathy, age-related macular degeneration, retinal vein occlusion, and retinopathy of prematurity.[3,4] It is thus a double-edged sword.[5] The humanized monoclonal antibody bevacizumab is one of the most popular anti-VEGF medications due to its relative efficacy and affordability. It has been used off-label since 2005.[6,7] In addition to more significant side effects including endophthalmitis and lens damage, frequent use of this medication may result in benign subconjunctival bleeding and corneal abrasion.[8]

Temporary and persistent elevation in intraocular pressure may result with intravitreal injections.[9] This study aimed to assess and quantify intraocular pressure alterations following intravitreal injection of bevacizumab for diabetic macular edema over a one-month period. This may help in planning post-injection management for these patients including vision preservation strategies due to raised IOP.

METHODS:

Study design, place & duration: This was a prospective cohort study conducted in The Layton Rahmatulla Benevolent Trust (LRBT) Tertiary Teaching Eye Hospital Korangi Karachi, from March 2023 to August 2023.

Ethical considerations: The study was approved by the Institutional review board / Ethical review board LRBT/TTEH/ERC/4503/13. Informed consent was taken from all the patients.

Inclusion criteria and exclusion criteria: Patients of both genders, above 18-years of age, diagnosed cases of type 2 diabetes mellitus with macular edema were included. Patients with glaucoma, those with a clinical history that suggested familial glaucoma, corneal thinning (less than 520 microns), were excluded, tractional retinal detachment, vitreomacular traction, ocular infection, uveitis, malignancy, and coronary artery disease, were excluded. Elevated intraocular pressure value was taken as above 21 mmHg.

Sample size estimation: It was calculated by Open epi calculator by taking mean IOP before injection equal to 18.0±5.9 mmHg and mean IOP after injection as 42.1±14.5 mmHg (Lemos-Reis R[10]), power of test as 80%. A sample size of 150 patients was taken for this study. A non-probability consecutive sampling technique was used.

Study protocol: After topical anesthesia, eyes were painted with 5% povidone iodine, Bevacizumab 0.05 mL(1.25mg) was administered by intravitreal injection using a 30-gauge needle via the pars plana, located inferotemporally, 3.5-4.0 mm from the limbus. Upon the needle insertion into the eye to a depth of 1.0-1.5 cm, the medication was administered. Intraocular pressure was measured using Goldmann applanation tonometry immediately post-injection, as well as after one-day, one-week and one- month. Postoperative treatment included the administration of topical antibiotics.

Statistical analysis: Analysis was conducted using SPSS Version 25. Descriptive statistics were employed to present the demographic data. Mean and standard deviation were used for quantitative variables. Qualitative variables were expressed as frequencies and percentages. Repeated measures of ANOVA test was employed to examine the mean change in intraocular pressure. Effect modifiers were controlled using stratification. Independent (student) t-test was applied for comparison of continuous variables (e.g., IOP, RNFL thickness, macular thickness) between two independent groups such as gender, age groups, and presence or absence of side effects. One-way ANOVA was used for comparing these variables across multiple diagnostic severity groups (very mild, mild, moderate, severe, and very severe). A significance criterion was $p<0.05$.

RESULTS:

Of total 150 patients; 82 (54.7%) were males and 68 (45.3%) females. Seventy-eight (52%) patients were =45-years of age. Fourteen (9.3%) individuals exhibited a very mild condition, whereas 69 (46%) presented with a light condition. Moderate and severe condition were noted in 21 (14%) participants each, whereas 25 (16.7%) patients had a very severe condition.

In table I measurements related to the macular thickness, retinal nerve fiber layer (RNFL) thickness, and intraocular pressure at various time points are presented. For macular thickness, there were no

Table I: Comparison of Thickness and Intraocular Pressure

	Macular thickness (micrometers)	RNFL thickness (micrometers)	IOP on admission (mmHg)	IOP immediately after injection (mmHg)	IOP after day-1 (mmHg)	IOP after week-1 (mmHg)	IOP after one-month (mmHg)
Overall	**477.03±43.46**	**95.88±3.99**	**18.68±4.02**	**24.23±3.98**	**20.67±4.03**	**16.99±3.39**	**16.44±3.37**
Diagnosis							
Very Mild	473.79±33.94	95.57±4.95	18.29±5.03	23.93±4.82	20.29±5.03	15.86±4.53	15.42±4.43
Mild	476.00±47.93	95.06±3.59	17.84±3.62	23.42±3.57	19.83±3.63	16.25±2.87	15.71±2.92
Moderate	483.62±41.89	95.52±3.94	18.43±3.89	23.95±3.96	20.43±3.89	17.05±3.76	16.33±3.65
Severe	480.24±39.28	96.00±3.64	18.95±3.72	24.38±3.76	20.95±3.72	17.67±3.49	17.23±3.40
Very Severe	473.48±42.12	98.52±3.95	21.20±4.11	26.72±4.06	23.20±4.11	19.08±2.79	18.48±2.81
p-value?	**0.929**	**0.006***	**0.009***	**0.011***	**0.009***	**0.003***	**0.004***
Side Effect							
Yes	480.08±43.62	98.02±3.73	20.80±3.80	26.22±3.79	22.80±3.80	18.92±3.04	13.84±3.09
No	475.55±43.52	94.84±3.70	17.65±3.74	23.26±3.72	19.64±3.74	16.06±3.16	15.52±3.11
p-value	**0.551**	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***

Independent t test was applied. ?One-way ANOVA was applied. p-value=0.05 considered as significant.
*Significant at 0.05 level.

Table II: Comparison of IOP (mmHg) at Various Time Intervals

	IOP on admission	IOP immediately after injection	IOP after day-1	IOP after week-1	IOP after one-month	p-value
Overall	18.68±4.02	24.23±3.98	20.67±4.03	16.99±3.39	16.44±3.37	<0.001*
Gender						
Male	18.16±4.15	24.16±4.15	20.15±4.16	16.72±3.44	16.13±3.39	<0.001*
Female	19.31±3.80	24.31±3.80	21.31±3.80	17.32±3.33	16.82±3.33	<0.001*
Age Group						
<45 years	18.17±4.04	23.77±3.95	20.15±4.05	16.46±3.34	15.94±3.26	<0.001*
>45 years	19.24±3.96	24.72±3.99	21.24±3.96	17.57±3.38	16.98±3.42	<0.001*
Diagnosis						
Very Mild	18.29±5.03	23.93±4.82	20.29±5.03	15.86±4.53	15.42±4.43	<0.001*
Mild	17.84±3.62	23.42±3.57	19.83±3.63	16.25±2.87	15.71±2.92	<0.001*
Moderate	18.43±3.89	23.95±3.96	20.43±3.89	17.05±3.76	16.33±3.65	<0.001*
Severe	18.95±3.72	24.38±3.76	20.95±3.72	17.67±3.49	17.23±3.40	<0.001*
Very Severe	21.20±4.11	26.72±4.06	23.20±4.11	19.08±2.79	18.48±2.81	<0.001*
Side Effect						
Yes	20.80±3.80	26.22±3.79	22.80±3.80	18.92±3.04	18.34±3.09	<0.001*
No	17.65±3.74	23.26±3.72	19.64±3.74	16.06±3.16	15.52±3.11	<0.001*

Repeated Measures of ANOVA p-value=0.05 considered as significant. *Significant at 0.05 level.

significant differences across the various levels of severity (p=0.929). However, RNFL thickness showed a significant difference between the severity groups (p = 0.006), with the highest RNFL thickness observed in the very severe group (98.52±3.95 micrometers) and the lowest in the mild group (95.06±3.59 micrometers).

Regarding IOP on admission, a significant difference was found across severity groups (p=0.009), with the very severe group having the highest value (21.20±4.11mmHg) and the mild group having the lowest value (17.84±3.62mmHg). IOP after administration of drug showed a significant difference (p=0.011), with the very severe group experiencing the highest pressure increase. At day-1, week-1, and one-month, there were statistically significant differences in IOP across the severity groups (p=0.009, 0.003, and 0.004, respectively). Adverse effects were reported by 49 (32.7%) patients. In terms of side effects, significant differences were observed between patients who experienced side effects across the groups (p<0.001). Significant differences were also found for stratified categories of gender, age groups, diagnosis and side effects as presented in table II.

DISCUSSION:

Diabetic macular edema is the primary cause of visual impairment in diabetic patients. One-third of diabetic individuals develop diabetic retinopathy, with 7% experiencing diabetic macular edema.[1] Our study showed promising outcome with the use of intravitreal bevacizumab. Another study showed also reported statistically significant outcome from baseline and noted a greater decrease in central macular thickness compared to glucagon-like peptide (GLP) treatment or bevacizumab combined with GLP therapy.[11] In index study five (5.7%) patients developed a transitory increase in IOP above 20 mmHg. This was treated conservatively with topical anti-glaucoma medicine.

In another study the likelihood of experiencing prolonged high IOP was 10% in the ranibizumab group compared to 3% in the sham group throughout a three-year follow-up period. The transient elevation in intraocular pressure may be attributed to a transitory increase in vitreous volume.[12] In our study four eyes had vitreomacular changes. Intravitreal anti-VEGF injections are now a recognized therapy for several retinal and choroidal disorders. A variety of anti-VEGF injections are utilized for these conditions. Bevacizumab is often utilized in low-middle-income countries due to its cost-effectiveness and accessibility.

A study by Lemos-Reis et al showed immediate post-injection intraocular pressure increases with a mean elevation of 28.6±13.8 mmHg without sub-conjunctival reflux compared to just 7.7±10.3 mmHg with reflux.[10] Kim et al also examined the immediate increase in intraocular pressure following anti-VEGF injection. However, their study employed different needle sizes for the injections of other medications, including ranibizumab and triamcinolone.[13] Another study demonstrated a significant negative linear connection between the axial length of the eyeball and the degree of elevated intraocular pressure in a cohort of 55 patients with diabetic macular edema treated with bevacizumab at a dosage of 1.25 mg. The post-injection intraocular pressure surge is often temporary, with pressure normalizing within a few hours following the injection.[14]

Proliferative diabetic retinopathy (PDR) patients has an average intraocular pressure of 28.94 mmHg at five minutes and 11.59 mmHg at six hours. The observed rise in intraocular pressure in these conditions is explained by the fact that diabetic macular edema accounted for 36.1% of the study's intravitreal injection indications, while proliferative diabetic retinopathy accounted for 18.8%.[5] This calls for more research in follow-up studies to develop long-term strategies for treating diabetic eye disease.

Limitations of the study: his was a single center study. The study population was also not uniform. This amounts to a selection bias. The follow up period was short. A multicenter prospective comparison trial with an extended follow-up to ascertain the efficacy and safety of the drug is recommended.

CONCLUSION:

The first delivery of bevacizumab injection may result in a temporary increase in intraocular pressure, which often subsides within a few hours.

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