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Effects of Intravitreal Injection of Ranibizumab on Intraocular Pressure

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ABSTRACT

Background: the administration of anti-vascular endothelial growth factor (anti-VEGF) agents has become an application of IVIs to treat a variety of retinal and choroidal neovascular diseases including neovascular age-related macular degeneration, vein occlusion with macular edema, and diabetic maculopathy. ranibizumab is the most commonly used anti-VEGF treatments for retinal disease. While Intravitreal ranibizumab appears to be safe and effective but it can cause adverse effects as intraocular inflammation, cataract, vitreous haemorrhage, and increased intraocular pressure.

Aim of the work: this study aimed to Evaluation of Iop changes after intravitreal injection of Ranibizumab retinal and choroidal neovascular diseases as neovascular age-related macular degeneration (AMD), central vein or branch vein occlusion with macular edema, and diabetic maculopathy

Patients and Methods: this prospective study was carried out from March 2018 to September 2018 on 35 eyes of patients attending outpatient clinic of Al-Azhar University Hospitals and Ophthalmology Department of Research Institute of Ophthalmology in Giza.

All participant names were hidden and were replaced by code numbers to maintain privacy of the patients. IOP was measured Using Applanation tonometer and Perkins tonometer before IVI of ranibizumab immediately after injection, 30 minutes, 1ST day, 1st week, and 1st month after injection.

Results: IOP was highly increased immediately after injection of ranibizumab, preoperative mean IOP 15.31±3.70, immediate after injection mean IOP 24.62±11.38, then it started to decrease till reaching normal values in the first 24h after injection, 1st 24hours mean IOP 16.31±3.60. The mean IOP for patients who were previously injected was 16.47±3.74 pre injection, and it was 30.88±12.55 immediately after injection, it still decreasing till reaching 20.24±2.77 after 30 minutes, we follow the patients after 1 day it was 18.41±3.12, then it became 18.29±3.62 after 1 week, and 17.88±3.33 after 1 month**.** The mean IOP for patients who were the first time to be injected was 14.22±3.41 pre injection, Immediate after injection the mean IOP was 18.72±5.92, after 30 minutes of injection the mean IOP was 15.44±3.99 mm Hg, after 1 day of injection the mean IOP was 14.33±2.87 mm Hg, We followed up the patients to one week after injection and we checked the IOP. The mean IOP after one week was 13.72±2.93mm Hg, We continue following the patients for one month and checked IOP, The mean IOP was 14.06±3.21 mm Hg**.**

Conclusion: IOP tends to increase after intravitreal injection of Ranibizumab 0.05ml (0.5 mg). It causes mainly a transient immediate increase in intraocular pressure especially in patients who exposed to repeated intravitreal injection. This elevation of IOP tends to normalize after one day.

Recommendations: this study recommend monitoring of IOP after intravitreal injection of ranibizumab and Care should be taken for cases with multiple injections and predisposing risk factors like glaucoma and glaucomatous patients

Keywords: Intravitreal injection, Ranibizumab, intraocular pressure.

INTRODUCTION

Intravitreal injection (IVI) therapy is getting more and more popular, The administration of anti-vascular endothelial growth factor (anti-VEGF) agents has become an application of IVIs to treat a variety of retinal and choroidal neovascular diseases including neovascular age-related macular degeneration ,central vein or branch vein occlusion with macular edema, and diabetic maculopathy [(1)].

All of these conditions are caused partly by over-production of a protein called vascular endothelial growth factor (VEGF). This protein was discovered in the 1980s and is important in the growth and development of blood vessels. VEGF production is increased by hypoxia (a lack of oxygen). So, if a tissue is not getting enough oxygen, it will produce more VEGF, which will stimulate the growth of additional blood vessels to provide more oxygen. In the presence of excessive VEGF, the capillaries start to leak and large molecules form exudates and escape into the retina

causing oedema in the surrounding tissues. If this affects the macula, then the central vision will be reduced, excessive VEGF also causes the growth of new, abnormal retinal blood vessels and capillaries. The new vessels are fragile and prone to tearing.

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When a new vessel is torn, it bleeds, causing vitreous haemorrhage. As the vitreous contracts, the new vessels pull on the retina, causing a traction retinal detachment and finally vision will be impaired[(2)]. Ranibizumab is the most commonly used anti-VEGF treatments for retinal disease. It has been FDA-approved for the treatment of diabetic retinopathy in DME, and wet-AMD, and macular edema in branch and central vein occlusions. Ranibizumab is a recombinant humanized IgG1 monoclonal antibody fragment that binds to and inhibits binding of vascular endothelial growth factor A molecules to their receptors on the surface of endothelial cells. Ranibizumab blocks all isoforms of VEGF-A. Each molecule of Ranibizumab has only one binding site for VEGF, which implies that two molecules of Ranibizumab are necessary to bind a VEGF Dimer [(3)]. While Intravitreal Ranibizumab appear to be safe and effective but it can cause adverse effects as intraocular inflammation, cataract, vitreous haemorrhage, and increased intraocular pressure [(4)]. Transient IOP elevation after anti-VEGF injection is considered to be related to a volume effect caused by the addition of fluid into the vitreous cavity [(5)]. Recent guidelines for intravitreal injections recommend "monitoring the IOP after injection and providing therapy when an elevated IOP warrants intervention, [(6)]. Patients with age related macular degeneration who received repeated intravitreal injections of anti VEGF have been reported that they had a risk of having glaucoma surgery as the end result of elevated intraocular pressure [(7)].

PATIENTS and METHODS

This is a prospective clinical study that carried out from March 2018 to September 2018 on 35 patients who are scheduled for unilateral intravitreal injection of ranibizumab .Cases were injected at Al-Azhar University hospitals (Al Hussein and Sayed Galal) and Research Institute of ophthalmology .

Inclusion criteria:

All patients scheduled for intravitreal injection of Ranibizumab because of diabetic macular edema, neovascular age-related macular degeneration (AMD), central vein or branch vein occlusion with macular edema, and active choroidal neovascularaization (CNV).

Exclusive criteria:

1.Patients previously were diagnosed as /having glaucoma, ocular hypertension or using anti glaucoma treatment.

2.Patients who underwent ocular surgeries as cataract less than 6 months, glaucoma surgery.

3.Patients with pigment dispersion, pseudoexfoliation or early iris neovascularization.

4.Patients with intraocular or extraocular inflammation.

5.Patients with significant corneal opacity that could interfere with proper standard Iop assessment.

All patients were subjected to the following:

***Preoperative assessment*:**

•History taking:

Personal data: name, age, sex, occupation, residency, etc.

Past ophthalmic history: last spectacle prescription, trauma, ocular surgery, and receiving ocular medication.

Present medical history: as diabetes and hypertension

•Visual acuity assessment: uncorrected and best corrected visual acuity.

•Slit lamp examination.

•Intraocular pressure measurement: IOP will be measured using Applanation tonometer attached to slit lamp.

•Gonioscopy: to evaluate angle using Goldman 3 mirror lens

•Fundus examination: using indirect ophthalmoscope, slit lamp biomicroscopy with 90 or 78 D lens after papillary dilatation with tropicamide 1% eye drops.

•Optical coherence tomography (OCT) and Fundus Fluorescein Angiography (FFA): were done for diagnosis and indications of intravitreal injection.

***Preoperative medications*:**

Topical eye drops 4th generation Quinolones was used for 48 hours prior to surgery five times daily.

Intravitreal injection of Ranibizumab:

Figure 1: ranibizumab (Lucentis) vial

All patients were injected by 0.5 mg (0.05 ml) of Ranibizumab.

***Technique of injection*:**

-application of topical mydriatic half an hour prior to injection using tropicamide 1% and cyclopentolate eye drops.

-Pupillary dilatation.

-Topical anaesthetic (Benoxinate 4%) and xylocaine 1% gel were applied to eye 5-10 minutes before injection.

-surgeon hand disinfection technique with sterile gloves.

- 5% povidone Iodine was instilled on the ocular surface and allowed adequate time (3 min.) prior to

injection.
-Periocular skin and eye lashes were sterilized with 5-10% povidone iodine.
-skin were dried and a sterile drape will be applied.
-Speculum insertion, marking site of injection with caliber (3, 5 ml from limbus in aphakic, pseudophakic patients and 3.5-4 ml from limbus in phakic patients).
-Application of 1-2 drops of single use antibiotic.
-Checking hand motion vision, fundus to ensure optic disc perfusion, ocular massage or paracentesis was done if not perfused till perfusion occurrence.
Post-operative IOP measurements:
-IOP was measured immediate after injection by using Perkins tonometer (figure 2).
-Then IOP was measured 30 minutes, 1st day, 7th day, 1st month after injection by Applanation tonometer.
-Sterilization of the cone before measurements of IOP for each patient.
-Sterile fluorescein strips were used for each patient.

Figure 2: Perkins tonometer

The study was done after approval of Ethical Board of Al-Azhar University and an informed written consent was taken from each participant in the study.
The results obtained were tabulated and statistically analyzed using IBM SPSS v21.0 statistical software (IBM Corporation, New York, USA).

RESULTS

Demographic data:

Age:
The mean age of our patients was 56.46±11.26 years.

Sex distribution:
There were 42.86% males and 57.14% females

Prevalence of retinal diseases among patients:
Out of 35 patients; 5 patients had myopic CNV (Choroidal neovascularization), 20 patients had DME (Diabetic macular edema), 3 patients had BRVO (Branch retinal vein occlusion), and 7 patients had Wet AMD (Age related macular degeneration (table 1).

Table (1): Prevalence of retinal diseases among patients

Disease	N	%
Myopic CNV	5	14.29
DME	20	54.14
NAMD	7	20.00
BRVO	3	8.57

Prevalence of patients injected before:
Out of 35 patients 18 were the first time to be injected and 17 were injected before (table 2).

Table (2): Prevalence of patients injected before among patients

	N	%
Injected before	17	48.57
Not Injected before	18	51.43

Descriptive data analysis:

*As regarding IOP:
Mean IOP before injection was 15.31±3.70 mm Hg, Immediate after injection the mean IOP was 24.63±11.39, after 30 minutes of injection the mean IOP was 17.77±4.18 mm Hg, after 1 day of injection the mean IOP was 16.31±3.60 mm Hg, We followed up the patients to one week after injection and we checked the IOP. The mean IOP after one week was 15.94±3.98 mm Hg**;** we continue following the patients for one month, the mean IOP after one month was 15.91±3.67 mm Hg (table 3, figure 3).

Table (3): Mean of intra ocular pressure changes after Ranibizumab (Lucentis) injection**.**

IOP	Mean ± SD
Pre-operative	15.31±3.70
Immediate after injection	24.62±11.38
Post-operative after 30 minutes	17.77±4.18
Post-operative after 1day	16.31±3.60
Post-operative after 1 week	15.94±3.98
Post-operative after 1month	15.91±3.76

*Relations between mean IOP during follow up period:
There was a highly statistically significant difference in mean IOP measured immediately after injection in comparison to mean pre operative value (p=0.001) (p value<0.05). There was a statistically significant difference in IOP measured after 30 minutes of injectio n(p=0.001) (p value<0.05). There was no statistically significant difference in IOP measured 1 day after injection1 week and 1 month (p value>0.05) table (4).

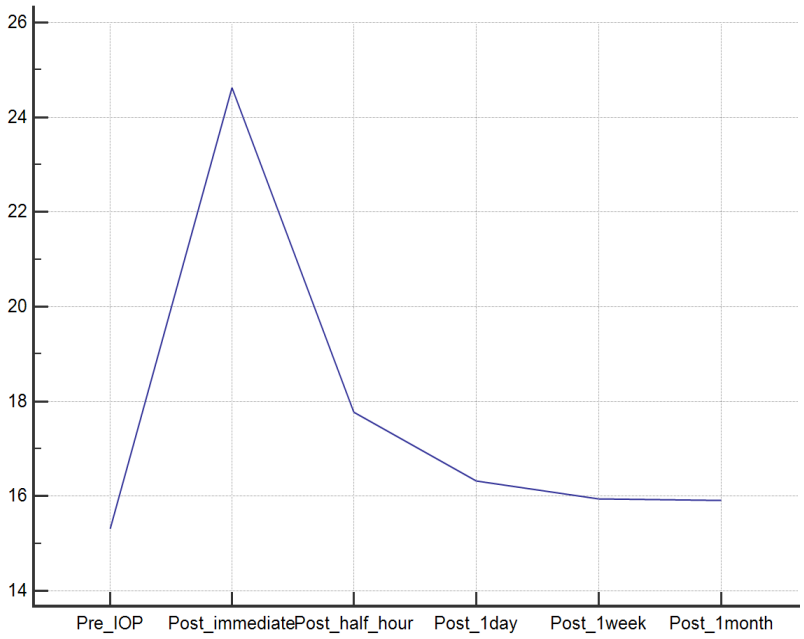

Figure 3: Mean of intra ocular pressure changes after Ranibizumab (Lucentis) injection.

Table (4) Comparison of significance between values of mean intraocular pressure before and after injection of ranibizumab

	Pre-operative	Post-operative Immediate	Post-operative after 30minutes	Post-operative after 1day	Post-operative after 1week	Post-operative after 1month
Mean ± SD	**15.31±3.70**	**24.62±11.39**	**17.77±4.18**	**16.31±3.60**	**15.94±3.98**	**15.91±3.76**
Significance between pre operative measures		**p<0.001**	**p<0.001**	**p>0.05**	**p>0.05**	**p>0.05**
Significance between post-operative immediately			**P=0.0036**	**P=0.0001**	**P<0.0001**	**P<0.0001**
Significance between 30minutes post-operative				**P=0.0003**	**P=0.0001**	**P=0.003**
Significance between 1day post-operative					**p>0.05**	**p>0.05**

P: probability **statistically significant (p<0.05)*

***As regarding IOP values according to history of previous injection**

Patients injected before:

The mean IOP for patients who were previously injected was 16.47±3.74 pre injection, and it was 30.88±12.55 immediately after injection, it still decreasing till reaching 20.24±2.77 after 30 minutes, we follow the patients after 1 day it was 18.41±3.12, then it became 18.29±3.62 after 1 week, and 17.88±3.33 after 1 month.

Patients injected for the first time:

The mean IOP for patients who were the first time to be injected was 14.22±3.41 pre injection, Immediate after injection the mean IOP was 18.72±5.92, after 30 minutes of injection the mean IOP was 15.44±3.99 mm Hg, after 1 day of injection the mean IOP was 14.33±2.87 mm Hg, We followed up the patients to one week after injection and we checked the IOP. The mean IOP after one week was 13.72±2.93mm Hg, We continue following the patients for one month and checked IOP, The mean IOP was 14.06±3.21 mm Hg table (5)

Table (5): Mean of intra ocular pressure changes after Ranibizumab (Lucentis) injection according to history

of injection

	Mean ± SD	
IOP measured	Injected before	First injection
Pre-operative	16.47±3.74	14.22±3.41
Immediate after injection	30.88±12.55	18.72±5.92
Post-operative after 30 minutes	20.24±2.77	15.44±3.99
Post-operative after 1day	18.41±3.12	14.33±2.87
Post-operative after 1 week	18.29±3.62	13.72±2.93
Post-operative after 1month	17.88±3.33	14.06±3.21

* Relation between IOP values according to history of previous injection:

As regarding IOP values for patients of repeated injection there was a statistically significant increase in mean values in immediate follow up when compared with immediate in patients who was the first time to be injected (p=0.005) (p<0.05) (figure 4).

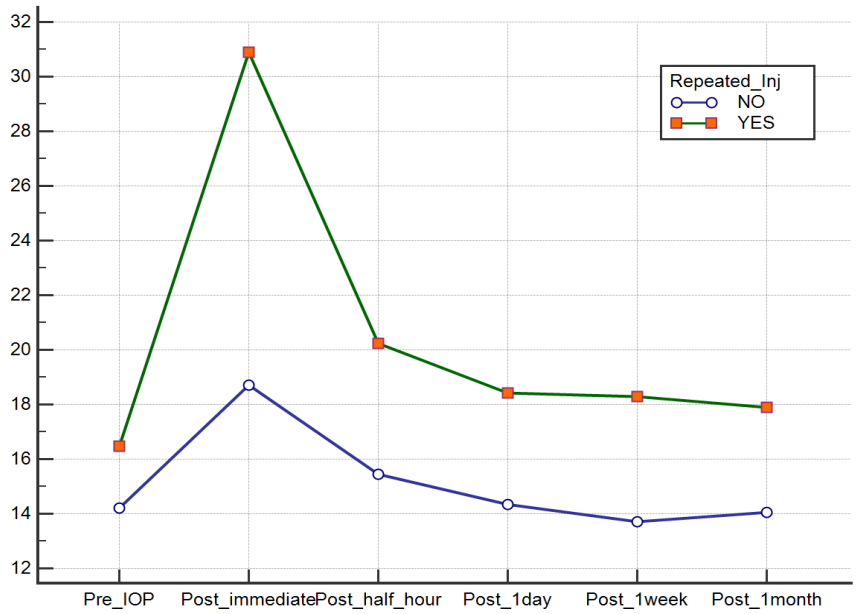

Figure 4: mean of IOP values after Intravitreal injection of ranibizumab according history of injection

DISCUSSION

Vascular endothelial growth factor (VEGF) and its receptors play an important role in many pathologic ocular processes. VEGF binding initiates an intracellular cascade that leads to proliferation and migration of vascular endothelial and eventually to neovascular angiogenesis. In addition to its role in neovascularization, VEGF increases vascular permeability and contributes to local inflammation. Selective blockade of this pathway was first employed clinically for the treatment of systemic oncologic processes. Ranibizumab is a specifically designed recombinant humanized antibody that binds and inhibits all biologically active VEGF isoforms[8].

Transient, short-term IOP elevation after intravitreal anti-VEGF therapy has been well described .The introduction of additional fluid into the vitreous cavity would be expected to cause an immediate rise in IOP. However, anti-VEGF therapy may also cause long-term, sustained IOP elevation [9].

Our study was conducted on 35 eyes who received 0.05 ml (0.5mg) of intravitreal Ranibizumab there were 15 Male (42.86%) and 20 Female (57.14%). The patients' age ranged from 17 to 74 years with a mean age 56.46±11.26 years.

Out of 35 patients, 5patients (14.29%) had myopic CNV, 20 patients (57.14%) had DME (Diabetic macular edema), 3 patients (8.57%) had BRVO, and 7

patients (20%) had Wet AMD. There were 18 of patients (51.43%) were the first time to be injected and 17 of patients (48.57%) were injected before.

We measured the IOP before the injection and immediate after injection using Perkins Tonometer and continue follow up patients after 30 minutes,1 day,1 week and 1 month using Goldman Applanation Tonometer

We found that IOP was highly increased immediately after injection of ranibizumab, preoperative mean IOP 15.31±3.70, immediate after injection mean IOP 24.62±11.38, then it started to decrease till reaching normal values in the first 24h after injection, 1st 24hours mean IOP 16.31±3.60.We also found that repeated intravitreal injection of ranibizumab was associated with increased IOP more than first time of injection.

The results of our study were comparable to a study done by Omay, et al.**(10)** to investigate the early effects of two intravitreal (IV) anti vascular endothelial growth factor agents (anti-VEGF), bevacizumab and ranibizumab, on intraocular pressure (IOP) within the first post-injection month. This study was conducted on 109 eyes that had IV bevacizumab or ranibizumab injections because of age-related macular degeneration (ARMD), retinal venous occlusion (RVO), diabetic retinopathy, and macular edema or central serous chorioretinopathy (CSCR). Iop was measured by Non-contact tonometer before injection and repeated at 30 min and 1st, 7th, and 30th day after the injection. Mean IOP before injection was 16.48 ± 4.39 (compared to our study 15.31±3.70), after 30 minutes the mean IOP was 22.02 ± 7.60 (compared to our study 17.77±4.18) after 1 day the mean IOP was 14.09 ± 4.42 (compared to our study 16.31±3.60), after 1 week it was 14.21 ± 4.24 (compared to our study 15.94±3.98), after 1 month it was 15.06 ± 4.62 (compared to our study 15.91±3.76). The IOP increased significantly 30 min after the injection ($p< 0.001$) but significant decreases were observed at the 1st, 7th, and 30th day post-injection ($p<0.001$).This results are comparable with our results that IOP increased 30 min after injection and it decreased at the 1st, 7th, and 30th day post injection but this study didn't observe IOP immediate after injection.

Another study also done by Lee etal which was done to investigate the effect of intravitreal anti-vascular endothothelial growth factor (ranibizumab or bevacizumab) injection on intraocular pressure, this study was conducted on 65 eyes , with diabetic macular edema, proliferative diabetic retinopathy-vitreous hemorrhage, exudative age-related macular degeneration, retinal vein occlusion-related macular edema, chronic central serous chorioretinopathy, and idiopathic choroidal neovascularization. IOP was measured by I care PRO rebound tonometer. Pre-injection mean IOP was 16.66 ± 3.50 mmHg (compared to our study 15.31±3.70), mean IOP was 43.81 ± 9.69 mmHg immediately after the injection (compared to our study 24.62±11.38), mean IOP was 17.57 ± 4.44 mmHg at 30 min (compared to our study 17.77±4.18), mean IOP was 15.00 ± 4.21 mmHg at 1 day (compared to our study 16.31±3.60), and mean IOP was 15.90 ± 3.63 mmHg at 1 week after the injection (compared to our study 15.94±3.98). It found that there was a significant increase in IOP immediately after injection which decreased to normal level within first 24 hours, This results are comparable with our results that IOP highly increased immediately after injection and it decreased at the 1st, 7th days post-injection, but mean IOP immediately after injection in our study (24.62±11.38) is relatively lower than this study(43.81 ± 9.69 mmHg) it may be due to small number of our study (35 cases) **(11).**

A study was done to evaluate effect of repeated intravitreal injection of Anti-VEGF on IOP; this study was conducted on 610 patients with active neovascular AMD, Goldman Applanation tonometry was performed monthly before treatment and in the studied eyes after injection. For every month of participation in the study, pre-injection IOP increased 0.02 mm Hg and post-injection IOP increased 0.03 mm Hg; both increases were statistically significant ($P < .001$ and $P = .002$, respectively) **(12).**

However a study done by Sobacı et al**(13)** to evaluate effect of multiple injections of ranibizumab on intraocular pressure (IOP) in patients with age-related macular degeneration (AMD), this study was conducted on 30 patients who were injected more than two injections IOP measurements were taken 30 minutes after each injection by Applanation tonometer , mean IOP before injection was 14.7±3.9 mmHg (compared to our study 16.47±3.74), mean IOP 30 minutes after injection was 16.1±2.3 mmHg (compared to our study 20.24±2.77) this study reported that repeated intravitreal injection of ranibizumab does not affect IOP in wet AMD patients, Our study differs from this study that we measured IOP immediately after injection of ranibizumab, while this study measured IOP 30 minutes after injection, so it ignored the critical period at which IOP is highly significant elevated.

CONCLUSION AND RECOMMENDATION

IOP tends to increase after intravitreal injection of Ranibizumab 0.05ml (0.5 mg). It causes mainly a transient immediate increase in intraocular pressure especially in patients who exposed to repeated

intravitreal injection. This elevation of IOP tends to normalize after one day. Acute elevation of IOP after intravitreal Ranibizumab is mainly related to acute increase in volume inside the eye and it takes 24 hours for this IOP to decrease to a normal level.

We recommend monitoring of IOP after intravitreal injection of ranibizumab and Care should be taken for cases with multiple injections and predisposing risk factors like glaucoma and glaucomatous patients

Our study has several limitations in terms of the small number of eyes studied and short period of follow up (only one month).

A prospective, controlled study including a large number of patients and a long term of period for follow up of the patients up are needed to further evaluate the effect of repeated intravitreal Ranibizumab on intraocular pressure.

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