



**Comparison between the Effect of Aflibercept (Eylea) and Ranibizumab (Lucentis) on Intraocular Pressure after 3<sup>rd</sup> Injection in Treatment of Diabetic Macular Edema**

*Dr. Hossam El Deen Mohamed Khalil, Dr. Ahmed Taha Gouda, Ibrahim Osama Ibrahim Abd Allah\**

Ophthalmology Department, Faculty of Medicine, Beni Suef University

**Abstract:**

**Background:** Currently, intravitreal injection of anti-VEGF is typically applied in the treatment of choroidal neovascularization (CNV), which occurs in patients with wet age-related macular degeneration (wAMD) and high myopia. It is also used to treat patients with macular edema secondary to diabetic retinopathy (DME) and retinal vein occlusions (RVO-ME). **Objectives:** This is a prospective, comparative clinical study between aflibercept (Eylea) and Ranibizumab (Lucentis) done to evaluate changes in intraocular pressure following 3<sup>rd</sup> intravitreal injection of different types of anti-VEGF agents used in patients presenting with proliferative diabetic retinopathy and diabetic macular edema and determine the need to monitor IOP after intravitreal injections of anti-VEGF agents. **Patients and Methods:** This is a prospective, comparative clinical study, that was conducted on 60 eyes of 60 patients. Patients scheduled for intravitreal injection of anti-VEGF 3 times were randomly divided into 2 groups: **Group A:** 30 eyes will be scheduled for intravitreal injection of ranibizumab (0.5 mg/0.05 ml) 3 times for the treatment of diabetic macular edema or proliferative diabetic retinopathy. Their mean age was (59.80±7.27 years), **Group B:** 30 eyes will be scheduled for intravitreal injection of aflibercept (2 mg/0.05 ml) 3 times for the treatment of diabetic macular edema or proliferative diabetic retinopathy. Their mean age was (59.83±6.29 years). **Results:** There is no significant difference between IOP after 1 week, 1 month and 2 months regarding ranibizumab and aflibercept, however, the range of decrease of IOP after one month regarding aflibercept was less than that of ranibizumab, accordingly, we can correlate this difference to the longer half life of aflibercept than that of ranibizumab. **Conclusion:** The current study confirms the results of previous studies which showed the safety of multiple IV injection of anti-VEGF agents for IOP elevation in post-injection first month in non glaucomatous patients. However, there might be a tendency to

increased IOP in glaucoma cases and repeated injections, so further studies about safety of repeated injections, in glaucomatous patients and for different retinal disorders should be carried out. Our study for intravitreal injections recommend “monitoring of IOP after injection and providing therapy when elevated IOP warrants intervention”.

**Keywords:** Aflibercept (Eylea), Ranibizumab (Lucentis), Diabetic Macular Edema

## 1. Introduction

Currently, intravitreal injection of anti-VEGF is typically applied in the treatment of choroidal neovascularization (CNV), which occurs in patients with wet age-related macular degeneration (wAMD) and high myopia. It is also used to treat patients with macular edema secondary to diabetic retinopathy (DME) and retinal vein occlusions (RVO-ME). Lucentis "Ranibizumab" (a recombinant, humanized monoclonal antibody targeting VEGF-A), and Eylea "aflibercept" (a soluble decoy receptor fusion protein), are commonly used for the treatment of CNV and macular edema. They both were approved by the Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products for the treatment <sup>(1,2,3)</sup>.

Despite the fact that the safety of these agents is generally approved by many physicians, some serious systemic and ocular complications can be seen after the injections. The reported ocular adverse effects include endophthalmitis, uveitis, cataract progression, vitreous hemorrhage, and retinal tears or

detachment. These ocular complications are reported in a very low rate (all <1%) <sup>(4)</sup>.

One side effect, which is controversially discussed to be associated with intravitreal anti-VEGF injections, is the rise in intraocular pressure (IOP). While intravitreal steroids are known to be associated with an increased risk for glaucoma, the data about IOP elevation by anti-VEGF agents are less conclusive. On rare occasions, it has been described that the IOP may increase transiently after intravitreal anti-VEGF injections, but returns to baseline level within 30 to 60 minutes without IOP-lowering therapy. This transient IOP elevation may result from introduction of additional fluid into the vitreous cavity by intravitreal therapy, variations in scleral rigidity or in reflux from the injection site after withdrawal of the needle <sup>(5,6,7)</sup>. The transient elevation of IOP is mainly related to acute volume expansion of the eyeball, which can be prevented by prophylactic anterior chamber paracentesis <sup>(8,9)</sup>.

The concept of normal intraocular pressure is defined by the distribution of the

IOP within the general population has a range of 11-21mmhg. Although there is no absolute pathological point, 21mmhg is considered the upper limit of normal and levels above this are viewed with suspicion. However in some patients glaucomatous damage occurs with IOPs less than 21mmhg (normal tension or normal pressure glaucoma) whilst others remain unscathed with IOP up to 30mmhg (ocular hypertension). Although the actual level of IOP is important in the development of glaucomatous damage, other factors are also significant.

Normal IOP varies with the time of day, heart beat, blood pressure level and respiration. The diurnal pattern varies, with a tendency to be higher in the morning and lower in the afternoon and evening. Normal eyes manifest a mean diurnal pressure variation of 5mmhg; Ocular hypertensive or glaucomatous eyes, however, exhibit a wider fluctuation. A single normal reading, particularly if taken during late afternoon, may therefore be misleading and it may be necessary to take several readings at different times of day ("phasing"). In clinical practice phasing during the normal hours may be sufficient because 80% of patients peak between 8:00 am and noon <sup>(10)</sup>.

Although some studies of IOP trends immediately after intravitreal injections of anti-VEGF agents concluded that monitoring of post-injection IOP may not be necessary, others suggest checking once at five to 10

minutes after injection, whereas others recommend IOP checking after injection but do not give guidance as to when or for how long. Herein, we sought to investigate the IOP trends after these commonly used intravitreal anti-VEGF agents and to explore factors that affect IOP changes after intravitreal anti-VEGF injections <sup>(11,12,13)</sup>.

## **2. Aim Of The Work**

This is a prospective, comparative clinical study between aflibercept (Eylea) and Ranibizumab (Lucentis) done to evaluate changes in intraocular pressure following 3rd intravitreal injection of different types of anti-VEGF agents used in patients presenting with proliferative diabetic retinopathy and diabetic macular edema and determine the need to monitor IOP after intravitreal injections of anti-VEGF agents.

## **3. Patients And Methods**

### **Study design**

This is a prospective, comparative clinical study, that was conducted on 60 eyes of 60 patients. Patients scheduled for intravitreal injection of anti-VEGF 3 times were randomly divided into 2 groups.

- **Group A:** 30 eyes will be scheduled for intravitreal injection of ranibizumab (0.5 mg/0.05 ml) 3 times for the treatment of diabetic macular edema or proliferative diabetic retinopathy. Their mean age was (59.80±7.27 years).

- **Group B:** 30 eyes will be scheduled for intravitreal injection of aflibercept (2 mg/0.05 ml) 3 times for the treatment of diabetic macular edema or proliferative diabetic retinopathy. Their mean age was (59.83±6.29 years).
- Patients which were diagnosed as having any type of glaucoma or ocular hypertension (IOP >21 mmHg), or using anti-glaucoma medications.
- Patients with medical histories of any ocular trauma or surgeries other than uncomplicated phacoemulsification and posterior chamber intraocular lens implantation.

**Criteria for Patient Selection (Inclusion criteria):**

- All patients who were scheduled for intravitreal injection of anti-VEGF because of diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR).
- Patients were randomly assigned to two groups. Group (A) will receive (0.5 mg/0.05 ml) of intravitreal ranibizumab and group (B) will receive (2 mg/0.05 ml) of intravitreal aflibercept.
- All patients should have normal IOP (10-21mm Hg) before the injection with no anti glaucoma medication.

**Exclusion Criteria:**

- Patients with intra-ocular inflammation or extra-ocular inflammation.
- Patients with previous intravitreal injections in the same eye within 6 months from initiation of the anti-VEGF therapy.
- Patients with significant corneal opacity that could interfere with proper standard IOP assessment and measurement such as glaucoma or corneal disease.

**Methodology**

All intravitreal injection of anti-VEGF were carried out at Egypt Air Hospital in Cairo in the period from January 2018 to July 2018. All patients included in the study from both groups were subjected to the following:

**Pre-Operative Assessment**

➤ **History Taking:**

- Personal data: age, sex, occupation, residency, etc.
- Ocular history and medical history of current medical disease

**Pre-Operative Examination**

**A complete ocular examination was done using the following:**

➤ **Visual Acuity Measurement:**

Uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA) were measured using Snellen chart.

➤ **Slit-Lamp Examination:**

Patients were subjected to slit lamp examination.

➤ **Intraocular Pressure Measurement:**

The IOP was measured using Goldman's applanation tonometer attached to the slit-lamp.

➤ **Gonioscopy:**

Was done to evaluate angle using Goldmann 3 mirror lens.

➤ **Fundus Examination:**

All patients underwent a thorough fundus examination using the indirect ophthalmoscope and slit lamp biomicroscopy with 90 D lens after pupillary dilatation with tropicamide 1% eye drops.

➤ **Optical coherence tomography(OCT) and Fundus Fluorescein Angiography (FFA):**

Were done for the diagnosis and indication for the intravitreal injection.

➤ **Pre-Operative Medications:**

Topical antibiotic eye drops 4<sup>th</sup> generation quinolones were used for 48 hours prior to surgery five times daily.

**Informed consent:**

The patients signed consent for intervention including their acceptance of advantages, disadvantages, risks of possible complications.

**Intravitreal injection of anti-VEGF steps:**

- A topical anaesthetic (Benoxinate 4% eye drops) was applied to the eye 5-10 minutes before the injection.

- A surgical hand disinfection technique with sterile gloves.
- 5% povidone iodine was instilled on to the ocular surface and allowed adequate time (3 minutes) prior to injection.
- Periocular skin and eyelid margins and eye lashes were cleaned with 5-10% povidone iodine.
- Skin was dried and a sterile drape was applied.
- Eyelid speculum was inserted, ensuring that it is well positioned underneath the eyelids to direct the eyelashes away from the field.
- Patient was instructed to direct gaze away from the site of injection.
- The scleral injection site was marked using the caliber (the entry site of the needle should be 3.0-3.5 mm from the limbus in aphakic/pseudophakic patients, and 3.5-4.0 mm in phakic patients. Avoid the horizontal meridians of the globe; although the infero-temporal quadrant is often used.
- By using the forceps to steady the eye, the needle is inserted tangentially to produce a tunnel through sclera to prevent reflux of vitreous or drug with the tip aimed towards the centre of the globe (to avoid any contact with the posterior lens).
- We applied 1-2 drops of single use antibiotic into treated eye.

- Checking hand motion vision was done to check optic disc perfusion.
- We used sterile fluorescein strips for each patient.

#### Post operative IOP measurement:

- Intra ocular pressure (IOP) will be measured using Goldmann applanation tonometer before the injection, 1 week after injection and 1 month after injection, 2 months after injection, whereas, IOP will be reported as the average of three reliable measures.
- Eyes were considered to have IOP elevation if they met any of the following criteria:
  - 1) An IOP rise to > 22 mmHg,
  - 2) An increase of 6 mmHg or more from baseline IOP, and /or
  - 3) A 20% rise from baseline IOP.
- Sterilization of the Goldmann applanation tonometer cone before measurement of IOP for each patient.

#### Statistical Analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when their distribution found parametric. Also qualitative variables were presented as number and percentages. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant at the level of < 0.05.

#### 4. Results:

**Table (1):** Comparison between lucentis group and eylea group regarding age.

Age	Lucentis group	Eylea group	Independent t-test		
	No. = 30	No. = 30	t	P-value	Sig.
Mean ± SD	57.73 ± 6.62	57.07 ± 5.74	0.417	0.678	NS
Range	45 – 68	47 – 66			

*P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant*

Table (1) shows that there is no significant difference between lucentis group and eylea group regarding age.

**Table (2):** Comparison between lucentis group and eylea group regarding gender.

Gender	Lucentis group	Eylea group	Chi-square test		
	No. (%)	No. (%)	X <sup>2</sup>	P-value	Sig.
Female	18 (60.0%)	16 (53.3%)	0.271	0.602	NS
Male	12 (40.0%)	14 (46.7%)			

*P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant*

Table (2) shows that there is no significant difference between lucentis group and eylea group regarding gender.

**Table (3):** Comparison between lucentis group and eylea group regarding IOP before injection.

Before injection	Lucentis group	Eylea group	Independent t-test		
	No. = 30	No. = 30	t	P-value	Sig.
Mean ± SD	16.50 ± 2.76	16.87 ± 2.40	-0.548	0.586	NS
Range	10 – 22	12 – 20			

*P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant*

Table (3) shows that there is no significant difference between lucentis group and eylea group regarding IOP before injection.

**Table (4):** Comparison between lucentis group and eylea group regarding IOP after 1 week of injection.

After 1 week	Lucentis group	Eylea group	Independent t-test		
	No. = 30	No. = 30	t	P-value	Sig.
Mean ± SD	18.53 ± 2.73	19.83 ± 3.56	-1.587	0.118	NS
Range	15 – 28	14 – 28			

*P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant*

Table (4) shows that there is no significant difference between lucentis group and eylea group regarding IOP after 1 week of injection.

**Table (5):** Comparison between lucentis group and eylea group regarding IOP after 1 month of injection.

After 1 month	Lucentis group	Eylea group	Independent t-test		
	No. = 30	No. = 30	t	P-value	Sig.
Mean ± SD	17.37 ± 2.48	18.47 ± 3.16	-1.499	0.139	NS
Range	13 – 25	11 – 26			

*P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant*

Table (5) shows that there is no significant difference between lucentis group and eylea group regarding IOP after 1 month of injection.

**Table (6):** Comparison between lucentis group and eylea group regarding IOP after 2 month of injection.

After 2 months	Lucentis group	Eylea group	Independent t-test		
	No. = 30	No. = 30	t	P-value	Sig.
Mean ± SD	16.70 ± 2.79	18.10 ± 3.62	-1.676	0.099	NS
Range	11 – 25	10 – 25			

*P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant*

Table (6) shows that there is no significant difference between lucentis group and eylea group regarding IOP after 2 month of injection.

**Table (7):** Comparison between pre-injection and postinjection values regarding lucentis

	Lucentis group	Mean difference	Paired t-test		
	Mean ± SD		t	P-value	Sig.
Before injection	16.50 ± 2.76	–	–	–	–
After 1 week	18.53 ± 2.73	-2.03	-3.238	0.003	HS
After 1 month	17.37 ± 2.48	-0.87	-1.396	0.173	NS
After 2 months	16.70 ± 2.79	-0.20	-0.312	0.757	NS

*P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant*



Table (7) shows the values of intraocular pressure before and after the injection of lucentis & that there is highly significant difference between the pre-injection and one week postinjection values.

**Table (8):** Comparison between pre-injection and postinjection values regarding eylea

	Eylea group	Mean difference	Paired t-test		
	Mean ± SD		t	P-value	Sig.
Before injection	16.87 ± 2.40	–	–	–	–
After 1 week	19.83 ± 3.56	2.97	-3.990	0.000	HS
After 1 month	18.47 ± 3.16	1.60	-2.091	0.045	S
After 2 months	18.10 ± 3.62	1.23	-1.448	0.158	NS

*P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant*

Table (8) shows the values of intraocular pressure before and after the injection of eylea & that there is significant difference between the pre-injection and postinjection values.

## 5. 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.

For patients with diabetic retinopathy, VEGF inhibitors seemed to be more effective as a short-term treatment option than alternative therapies, however, the evidence is not of sufficient quality to confirm safety<sup>(14)</sup>.

Moreover, the incidences of serious ocular and non ocular adverse events are approximately below 1 per 100 injections for intravitreal bevacizumab, intravitreal ranibizumab, and intravitreal pegaptanib<sup>(4)</sup>.

While agents like aflibercept and ranibizumab appear to be safe and effective, there have been reports of sustained elevation of intraocular pressure (IOP) after single or multiple intravitreal injections of these protein-based therapeutics, whereas, the true mechanism leading to sustained spikes in IOP remains unknown<sup>(15,16)</sup>.

Several theories regarding possible mechanisms of how intravitreal anti-VEGF

injections could lead to sustained IOP elevation include a pharmacologic effect of VEGF blockade, an inflammatory mechanism/trabeculitis, impaired outflow due to protein aggregates/silicone droplet debris, and damage to outflow pathways due to the repeated trauma and/or IOP spikes associated with the injection procedure. Specifically, Good et al., reported that 33% of 21 patients in a glaucoma subgroup experienced sustained elevated IOP after fewer injections. This was attributed to a likely preexistent compromise in aqueous humor outflow facility<sup>(17)</sup>. Adelman et al., proposed that anti-VEGF injections may decrease trabecular meshwork function, either mechanically or physiologically<sup>(18)</sup>, but Kernt et al., reported no in vivo toxicity to the trabecular meshwork with standard concentrations of bevacizumab<sup>(19)</sup>.

Also, an increase in concentration of aqueous humor protein has been associated with elevated IOP in uveitis<sup>(20)</sup>. It has been suggested that an immunologic reaction may be induced by anti-VEGF agents, resulting in inflammation and subsequent IOP elevation<sup>(21)</sup>. Good et al., noted a difference in rates of sustained IOP elevation between two different study centers and suggested that this may be because of differences in the way pharmacies and clinics prepare, ship, and store prefilled bevacizumab syringes or different injection techniques<sup>(17)</sup>.

Additionally, it has been suggested that a disruption of the anterior hyaloid or zonules may allow access for high-molecular weight proteins to enter the anterior chamber and result in ocular hypertension. Multiple doses of these proteins may mechanically or physiologically disrupt the normal aqueous humor outflow<sup>(18)</sup>. Others have theorized that silicone oil used to lubricate the components of syringes or the accumulation of protein aggregates may play a role in these sustained IOP elevations<sup>(14,22)</sup>.

Additionally, a recent report noted decreased binding affinity of ranibizumab after storage in plastic syringes versus original vials. Meyer et al., also noted a significant variance in the accuracy, precision, and repeatability to the manual approach to prepare a proposed dose of intravitreal ranibizumab. There may also be a connection between IOP and genomic mutations<sup>(23)</sup>.

Generally a transient elevation occurs because of injected 0.05 cc volume of anti-VEGF agent within the first post-injection hour and decreases in 24 h<sup>(12,13)</sup>, but recent reports suggest that sustained ocular hypertension after intravitreal anti-VEGF treatment is also possible<sup>(17,24,25)</sup>.

Our study was conducted on 60 eyes of 60 patients, we aimed to investigate the effects of intravitreally injected anti-VEGF agents on IOP within the two months post-injection in the cases subjected to 3 times injection for

diabetic macular edema & proliferative diabetic retinopathy. We excluded the cases with neovascular glaucoma (NVG) and other types of glaucoma in order to eliminate the effect of glaucoma on IOP values at the first week, first month and 2nd month after the 3rd injection.

**They were randomly divided into 2 groups:**

➤ **In group A:**

30 eyes of 30 patients: 20 patients had DME (Diabetic macular edema), 10 patients had PDR (Proliferative diabetic retinopathy). They received (0.5 mg/0.05 ml) of intravitreal injection of ranibizumab. There were 18 Female and 12 Male patients with a mean age  $57.73 \pm 6.62$  years (range from 45 – 68).

➤ **In group B:**

30 eyes of 30 patients: 22 patients had DME (Diabetic macular edema), 8 patients had PDR (Proliferative diabetic retinopathy). They received (2 mg/0.05 ml) of intravitreal injection of aflibercept. There were 16 Female and 14 Male patients with a mean age  $57.07 \pm 5.74$  years (range 47 – 66).

We measured the IOP by Goldmann tonometer. In comparison between IOP regarding ranibizumab and aflibercept.

The mean IOP before the injection in group (A) was  $16.50 \pm 2.76$  mmHg; and in group (B) mean IOP was  $16.87 \pm 2.40$  mmHg. There was no significant difference in IOP

between the two studied groups before the injection ( $p = 0.586$ ) ( $p \text{ value} > 0.05$ ).

At 1 week after injection the mean IOP in group (A) was  $18.53 \pm 2.73$  mmHg; and in group (B) mean IOP was  $19.83 \pm 3.56$  mmHg. There was no significant difference in IOP measured 1 week after injection between the two studied groups ( $p = 0.118$ ) ( $p \text{ value} > 0.05$ ). The difference from the baseline IOP in group (A) was  $2.03 \pm 2.73$  mmHg; and in group (B) was  $2.97 \pm 3.56$  mmHg. There was highly significant increase in IOP measured 1 week after injection from the baseline IOP.

At one month after injection the mean IOP in group (A) was  $17.37 \pm 2.48$  mm Hg; and in group (B) mean IOP was  $18.47 \pm 3.16$  mm Hg. There was no significant difference in IOP measured 1 month after injection between the two studied groups ( $p = 0.139$ ) ( $p \text{ value} > 0.05$ ). The difference from the baseline IOP in group (A) was  $0.87 \pm 2.48$  mmHg; and in group (B) was  $1.60 \pm 3.16$  mmHg. There was significant increase in IOP measured one month after injection from the baseline IOP in group (B).

At two months after injection the mean IOP in group (A) was  $16.70 \pm 2.79$  mm Hg; and in group (B) mean IOP was  $16.70 \pm 2.79$  mm Hg. There was no significant difference in IOP measured 2 month after injection between the two studied groups ( $p = 0.099$ ) ( $p \text{ value} > 0.05$ ). The difference from the baseline IOP in group (A) was  $0.20 \pm 2.79$

mmHg; and in group (B) was  $1.23 \pm 3.62$ mmHg. There was no significant increase in IOP measured 2 month after injection from the baseline IOP.

So our study shows that there is no significant difference between IOP after 1 week, 1 month and 2 months regarding ranibizumab and aflibercept, however, the range of decrease of IOP after one month regarding aflibercept was less than that of ranibizumab, accordingly, we can correlate this difference to the longer half life of aflibercept than that of ranibizumab.

Most of our results were comparable to the most recent studies. The first one was retrospective study done to investigate elevated intraocular pressures (IOP) (defined by a measurement  $>25$  mmHg at a follow-up visit) after an intravitreal injection of anti-vascular endothelial growth factor agents for age-related macular degeneration. A total of 127 patients (155 eyes) received an intravitreal injection of anti-vascular endothelial growth factor agents (bevacizumab, ranibizumab, or pegaptanib) ranging from 1 to 39 injections for more than a period of 30 to 1759 days. Among this population, 12 patients (14 eyes; 9.4%) developed elevated IOP  $>25$  mmHg. Of these, 7 patients (5.5%) developed sustained elevated IOP (IOP  $>25$  mmHg on 2 separate visits requiring glaucoma medication or surgery), of which 8 eyes required topical medications and 1 eye underwent glaucoma

surgery. Mean IOP of injected eyes receiving intravitreal injection was  $15.2 \pm 2.4$  mmHg, and the mean IOP was  $14.9 \pm 2.6$  mmHg for noninjected eyes. Among eyes that had elevated IOPs, there was no association with injection frequency, number of injections, or anti-vascular endothelial growth factor agent used <sup>(26)</sup>.

The 1<sup>st</sup> difference of our study compared with the study by *Choi et al.* is indication of injection as Diabetic retinopathy (indication of our study) is the most common indication for intravitreal anti-VEGF therapy in our institution; therefore, it was intriguing to assess whether IOP elevation after such therapy is an issue in Diabetic retinopathy patients as has been reported for NVAMD. The 2<sup>nd</sup> difference is age at presentation between patients with NVAMD and Diabetic retinopathy, which was clearly lower in this study compared with that in previous NVAMD reports. For example, the mean age in this study was 57.73 years (SD  $\approx 6.62$ ) compared with the study by *Choi et al.*, who reported a mean age of 81 years (SD, 10) in their patients with NVAMD <sup>(26)</sup>. As age is a significant risk factor for IOP elevation and open-angle glaucoma, a careful analysis of the confounding effect of age on the incidence of IOP elevation after anti-VEGF therapy should be undertaken particularly in an elderly population like patients with NVAMD <sup>(27)</sup>. The 3<sup>rd</sup> difference is *Choi et al.*, is

retrospective study assesses IOP after multiple anti-VEGF injections but aflibercept not included<sup>(26)</sup>.

According to these differences there are also differences in results between our study and *Choi et al.*

Another study was done to investigate the early effects of two intravitreal (IV) anti-vascular endothelial growth factor agents (anti-VEGF), bevacizumab and ranibizumab, on intraocular pressure (IOP) and central corneal thickness (CCT) within the first post-injection month. This prospective study comprised 109 eyes of 109 adult cases who 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). None of the cases had medical histories of any kinds of glaucoma or increased IOP and IV injection before and all of them underwent a detailed ocular examination including measurements of IOP by non-contact tonometer and CCT by ultrasonic pachymeter pre-injection. IOP measurements were repeated at 30 min and 1st, 7th, and 30th day after the injection. CCT measurements were repeated at the 7th and 30th post-injection day. Paired sample *t* tests were used for the statistical analysis in order to evaluate the significance of changes in IOP and CCT. The mean age of 56 male and 53 female cases was  $63.58 \pm 11.04$  years. Fifty-

six cases (51.4 %) had diabetic retinopathy, 33 cases (30.3 %) had ARMD, 11 cases (10.1 %) had RVO, and 9 cases (8.3 %) had CSCR. Bevacizumab was used in 97 (89 %) cases and ranibizumab was used in 12 (11 %) cases. The IOP increased significantly 30 min after the injection ( $p < 0.001$ ) but significant decreases were observed at the 1<sup>st</sup>, 7<sup>th</sup>, and 30<sup>th</sup> day post-injection ( $p < 0.001$ ). No significant differences were observed in CCT between pre-injection and 7th and 30th post-injection day values ( $p = 0.924$  and  $p = 0.589$ , respectively). Intravitreal bevacizumab and ranibizumab injections can cause hyper acute increase in IOP because of vitreal expansion but this effect is generally reversible in non-glaucomatous cases<sup>(28)</sup>.

Our study was similar to this study in significant decreased of mean IOP in 1<sup>st</sup> month after injection of ranibizumab .

The strength of the current study is its prospective design. The limitations include the average sample size, the short duration of follow-up and the lack of control group.

## 6. Conclusion:

In conclusion, the current study confirms the results of previous studies which showed the safety of multiple IV injection of anti-VEGF agents for IOP elevation in post-injection first month in non glaucomatous patients. However, there might be a tendency to increased IOP in glaucoma cases and repeated injections, so further studies about

safety of repeated injections, in glaucomatous patients and for different retinal disorders should be carried out. Our study for intravitreal injections recommend “monitoring of IOP after injection and providing therapy when elevated IOP warrants intervention”.

## **7. References:**

1. Catt Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med.* 2011; 364: 1897–908.
2. Heier JS, David MB, Victor C, Jean-Francois K, Peter KK, Quan DN, Bernd K, Allen H, Yuichiro O, George DY et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology.* 2012; 119: 2537–48.
3. Heier JS, Antoszyk AN, Pavan PR, et al. (2006): Ranibizumab for treatment of neovascular age-related macular degeneration: a phase I/II multicenter, controlled, multidose study. *Ophthalmology;* 113(4):633, e1-4.
4. Van der Reis MI, La Heij EC et al. (2011): A systematic review of the adverse events of intravitreal anti-vascular endothelial growth factor injections. *Retina;* 31:1449–1469.
5. Hollands H, Wong J, Bruemner R et al. (2007): Short-term intraocular pressure changes after intravitreal injection of bevacizumab. *Can J Ophthalmol;* 42:807–811.
6. Mojica G, Hariprasad SM, Jager RD et al. (2008): Short-term intraocular pressure trends following intravitreal injections of ranibizumab (Lucentis) for the treatment of wet age-related macular degeneration. *Br J Ophthalmol.;* 92(4):584.
7. Sharei V, Hohn F, Kohler T, et al. (2010): Course of Intraocular Pressure after Intravitreal Injection of 0.05 mL Ranibizumab (Lucentis). *European Journal of Ophthalmology,* 2010; 20, 174-179.
8. Knip MM and Välimäki J. Effects of pegaptanib injections on intraocular pressure with and without anterior chamber paracentesis: a prospective study. *Acta ophthalmologica.* 2012; 90: 254–8.
9. Kotliar K, Mathias M, Svetlana B, Nikolaus F, Chris L, Ines L et al. Effect of intravitreal injections and volume changes on intraocular pressure: clinical results and biomechanical model. *Acta Ophthalmol Scand.* 2007; 85: 777–81.
10. Jack JK. Brad Bowling, Seventh Edition, 2012; pp: 312.

11. Gismondi M, Salati C, Salvetat ML et al. (2009): Short-term effect of intravitreal injection of ranibizumab (Lucentis) on intraocular pressure. *J Glaucoma*; 18:658–661.
12. Abedi G, Adelman RA and Salim S (2013): Incidence and management of elevated intraocular pressure with antivascular endothelial growth factor agents. *Semin Ophthalmol*; 28:126–130.
13. Lemos-Reis R, Moreira-Gonc, et al. (2014): Immediate effect of intravitreal injection of bevacizumab on intraocular pressure. *Clin Ophthalmol*; 23:1383–1388.
14. Sniegowski M, Mandava N and Kahook MY, (2010): Sustained intraocular pressure elevation after intravitreal injection of bevacizumab and ranibizumab associated with trabeculitis. *Open Ophthalmol J*; 4:28–29.
15. Morshedi RG, Ricca AM and Wirostko BM (2014): Ocular hypertension following intravitreal antivascular endothelial growth factor therapy: review of the literature and possible role of nitric oxide. *J Glaucoma* (Epub ahead of print)
16. SooHoo JR, Seibold LK and Kahook MY (2014): The link between intravitreal antivascular endothelial growth factor injections and glaucoma. *Curr Opin Ophthalmol*; 25:127–133.
17. Good TJ, Kimura AE et al. (2011): Sustained elevation of intraocular pressure after intravitreal injections of anti-VEGF agents. *Br J Ophthalmol*; 95(8):1111-4.
18. Adelman RA, Zheng Q, Mayer HR (2010): Persistent ocular hypertension following intravitreal bevacizumab and ranibizumab injections. *J OculPharmacolTher*; 26:105–110.
19. Kernt M, Welge-Lüssen U, Yu A, et al. (2007): Bevacizumab is not toxic to human anterior- and posterior-segment cultured cells. *Ophthalmologe*; 104:965–971.
20. Ladas JG, Yu F, Davis JL, et al. (2001): Relationship between aqueous humor protein level and outflow facility in patients with uveitis. *Invest Ophthalmol Vis Sci*; 42:2584e8.
21. Georgopoulos M, Polak K, Prager F et al. (2009): Characteristics of severe intraocular inflammation following intravitreal injection of bevacizumab (Avastin). *British Journal of Ophthalmology*; 93(4):457–462.
22. Liu L, Ammar DA, Ross LA, et al. (2011): Silicone oil microdroplets and protein aggregates in repackaged bevacizumab and ranibizumab: effects of long-term storage and product mishandling. *Invest Ophthalmol Vis Sci*; 2:1023–1034.

23. Meyer CH, Liu Z, Brinkmann C, et al. (2011): Accuracy, precision and repeatability in preparing the intravitreal dose with a 1.0-cc syringe. *Acta Ophthalmol* 2011. Epub ahead of print.
24. Bakri SJ, McCannel CA, Edwards AO, et al. (2008): Persistent ocular hypertension following intravitreal ranibizumab. *Graefes Arch Clin Exp Ophthalmol*; 246:955–958.
25. Kahook MY, Kimura AE, Wong LJ et al. (2009): Sustained elevation in intraocular pressure associated with intravitreal bevacizumab injections. *Ophthalmic Surg Lasers Imaging*; 40: 293-5.
26. Choi DY, Ortube MC, McCannel CA, et al. (2011): Sustained elevated intraocular pressures after intravitreal injection of bevacizumab, ranibizumab, and pegaptanib. *Retina.*; 31(6): 1028-35.
27. Quigley HA and Broman AT (2006): The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*; 90: 262–267.
28. Omay E, Elgin U, Sen E et al. (2016): The early effects of intravitreal anti vascular endothelial growth factor agents on intraocular pressure and central corneal thickness *Int Ophthalmol*; 36: 665.