ORIGINAL ARTICLE

Changes of Ocular Biometry and Intraocular Pressure in Patients Treated With Intravitreal Injection of Antivascular Endothelial Growth Factors

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ABSTRACT

Introduction: Anti-vascular endothelial growth factors (anti-VEGF) intravitreal injection is one of the popular procedures for medical retina diseases. However, the incidence of angle-closure post intravitreal injection was reported. Several similar studies were conducted previously, but the results were inconsistent and mostly focused on bevacizumab. **Methods:** A prospective cohort study was conducted. After informed consent, patients who were more than 17 years old and received the first intravitreal anti-VEGF injections (ranibizumab or aflibercept) were recruited. Exclusion criteria included patients with underlying glaucoma, ocular hypertension, intumescence cataract, high refractive error or those with history of intraocular operation or ocular trauma. Pre- and post-injection's intraocular pressure (IOP) and ocular biometry included "central anterior chamber depth" (CACD), "angle opening distance" (AOD500), and "trabeculo-iris angle" (TIA500) at nasal and temporal 500 µm away the scleral spur were acquired and analyzed. **Results:** 72 eyes from 66 patients were studied. Mean (SD) increment of IOP following injection within 30 minutes and 1 hour were 6.16 (0.68) mmHg ($p<0.001$) and 1.26 (0.35) mmHg ($p=0.002$) respectively. Mean (SD) differences of temporal TIA500 between pre with within 30 minutes and 1-hour post-injection were 1.66 (0.66) degrees ($p=0.04$) and 1.45 (0.57) degrees ($p=0.04$) respectively. No significant relationship between the changes of IOP and ocular biometry was found. **Conclusion:** A single dose of anti-VEGF in a normal population is relatively safe. However, concern on the risk of glaucoma progression and acute angle-closure still needs to be addressed. Further studies on at-risk populations and repeated injections are useful.
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INTRODUCTION

Intravitreal injection of anti-vascular endothelial growth factors (anti-VEGF) is getting more and more popular nowadays (1). In United States, several million anti-VEGF injections are administered every year and this number is still increasing each year (2). Placental growth factor (PLGF), VEGF A, VEGF B, VEGF C, VEGF D, and VEGF E are the six proteins described in the family of vascular endothelial growth factor (VEGF) (3), and these VEGF factors are believed to have a vital role in the progression of age-related macular degeneration as well other aetiologies of choroidal neovascularisation such as retinal vein occlusion, pathological myopia, and uveitis (4, 5). Thus, inhibiting the activity of VEGF is believed to be able to control the progression of neovascularisation in age-related macular degeneration (AMD). The available anti-VEGF are pegaptanib, bevacizumab, ranibizumab, and aflibercept (4).

Meanwhile, several ocular and systemic complications following intravitreal injection of anti-VEGF are reported so far, of which the increase in intraocular pressure was found to be one of the most common confounding ocular complications. The other ocular complications such as infectious uveitis, retinal detachment, and subretinal haemorrhage also been reported (6).

Intraocular pressure (IOP) is defined as the fluid pressure within the eye and it can be measured by the force applied by the aqueous fluid on the cornea. Theoretically, IOP is explained by Goldmann equation, in which IOP equal to [F (aqueous flow rate) / C (aqueous outflow)]

+ P (episcleral venous pressure). Meaning that, IOP will be alter by any fluctuation on these variables (7). Nevertheless, other ocular biometry such as the anterior chamber depth also influences the IOP (8).

Sudden rise of high IOP would almost inevitably cause variable degree of mechanical injury and ischemic stress on the retinal nerve fiber layer (RNFL) if left untreated (7) , and this explained the main pathogenesis of progressive irreversible glaucoma especially in those with chronic elevation of IOP. Besides, the increase of oxidative stress and chronic inflammation have also been demonstrated in ocular hypertensive eye, which consequently causing irreversible tissue damage on retina and optic nerve (9). Even though only small volume of intravitreal anti-VEGF injection (which only 50µl) was given, immediate acute rise of high IOP post-injection has been reported, which contribute to acute symptoms of ocular pain and vision loss (10, 11).

Unfortunately, only limited studies available on ocular biometry following intravitreal injection of anti-VEGF, particularly on aflibercept or ranibizumab, and it mainly involving Caucasians population. Also, variable ocular biometric parameters were reported between Caucasians and Asians, where greater angle recess area, anterior chamber width, iris curvature and thickness were found among Caucasians as compared to Chinese population (12). No similar study was conducted on the perspective of biometry changes in Malaysia and limited study in Asian countries. Furthermore, variable baseline IOP was identified among different ethnicity as well, of which Chua J et al from Singapore reported of mean IOP of 14.3±3.1 mmHg, 15.3±3.7 mmHg, and 15.8±2.9 mmHg among the Chinese, Malay, and Indian participants respectively (12).

This urge for local studies for better understanding regarding the ocular biometry changes and risk of developing high IOP following intravitreal injection of anti-VEGF among our local multiracial population. This study also aimed to create awareness in spike of IOP post anti-VEGF and guide the clinician's decision on prescribing IOP lowering drug pre- or post-intravitreal injection of anti-VEGF, to prevent acute angle-closure attack especially in at-risk population.

MATERIALS AND METHODS

This is a prospective cohort study conducted in Hospital Raja Permaisuri Bainun (HRPB) Perak, Malaysia from May 2020 to May 2021. Ethical approval was achieved from the research ethics committee of the School of Medical Sciences, Universiti Sains Malaysia [USM/JEPeM/20020102] and the National Medical Research Register [NMRR-19-3940-50159] in accordance with the Helsinki Declaration on Human Research.

To determine the IOP and ocular biometry changes within 30 minutes and 1 hour post intravitreal injection of anti-VEGF, the sample size was calculated using G-power, F test, repeated measure ANOVA with the effect size of 0.25, α error of 0.05 and the power of 0.80. with the minimal sample size required was 28 eyes. As for second objective, the determination of relationship of ocular biometry changes with IOP changes post intravitreal injection of anti-VEGF, a minimum sample size of 65 eyes was required, calculated using G-power, multiple linear regress, F test with the same effect size, α error and power as first objective. 10 percent of dropout rate was considered in this study, and thus we concluded that a minimum sample size of 72 eyes is required for a statistically significant outcome.

At Hospital Raja Permaisuri Bainun Ipoh, patients who required intravitreal treatment of anti-VEGF injection for various pathology will be scheduled as daycare procedure at appointed date. Those potential subjects who fulfilled both the inclusion, and exclusion criteria for the study were identified during pre-procedure screening and were invited to join the research. The inclusion criteria include patients of age more than 17 years old who receiving the first dose of intravitreal anti-VEGF. On the other hand, patients with underlying glaucoma, ocular hypertension, or intumescence cataract, history of intraocular surgery or ocular trauma, and refractive error with more than +/-4D were excluded from the study.

After the recruitment of subjects, potential patients were invited to consultation room, and the purpose of the study, participants criteria, study procedures, risk of participation, and safety assessment of the study were explained. Written detailed information was provided to the selected subjects, and written consents were taken from those consented.

Before injection, the baseline IOP of all subjects were checked using tonopen (Tonopen XL Reichert Technologies), a portable and easy-handle device which cause minimal discomfort to the patient, but yet with high specificity and negative predictive value (13). Refraction was measured using automated keratometer refraction (Topcon KR-8900) and ocular biometry using Visante "anterior segment-optical coherence tomography" (AS-OCT). All parameters were obtained by same assigned well-trained paramedic to reduce the bias.

During the procedure, patients were lied flat in the treatment room, and intravitreal injection of 0.05mls of either aflibercept or ranibizumab (anti-VEGF) was given to the patients using direct injection method at superotemporal quadrant 4mm from limbus into vitreous as planned. Post procedure, patients were then allowed to sit up and rest in the daycare clinic while waiting for reassessment and measurement of IOP and ocular biometry within 30 minutes and 1 hour after the intravitreal injection.

The following ocular biometric parameters were measured using AS-OCT:

1. Central anterior chamber depth (CACD): This is determined by drawing a line perpendicularly from the central of cornea at endothelium level toward the anterior surface of anterior capsule of the lens (Fig. 1).
2. Trabeculo-iris angle (TIA): An angle formed by the arms of an angle running perpendicularly between a point on the trabecular meshwork 500 µm from the scleral spur and a point on the iris (Fig. 1 and 2).
3. Angle opening distance (AOD): The distance between the corneal endothelium and the anterior iris surface was measured perpendicular to a line drawn 500 µm from the scleral spur (Fig 2).

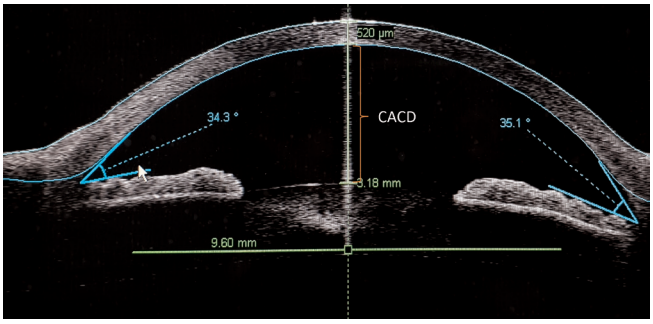

Fig. 1: Central anterior chamber depth (CACD) and trabecular iris angle 500 (white arrow)

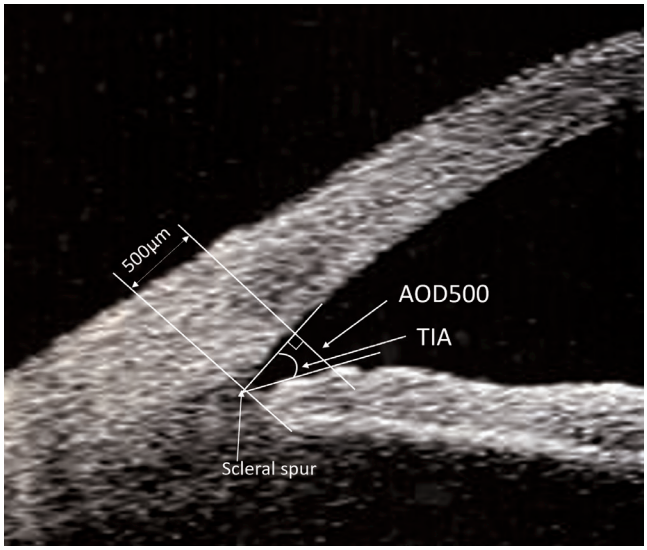

Fig. 2: Angle opening distance 500 (AOD500) and trabecular-iris angle (TIA)

Statistical data was analyzed using IBM Statistical Package for Social Sciences (SPSS) version 26.0. The changes of IOP, CACD, TIA500 (nasal and temporal), and AOD500 (nasal and temporal) at the baseline, within 30 minutes, and 1-hour post intravitreal injection of anti-VEGF were evaluated by repeated-measures analysis of variance (RM ANOVA) within group. A simple-linear and multiple-linear regression analysis was created to study the relationship of the ocular biometry (CACD, TIA500, AOD500) with the IOP difference at baseline, within 30 minutes and 1-hour after intravitreal injection. Statistical significance was achieved as if a p-value of less than 0.05 obtained.

RESULTS

Demographic Data

Seventy-two eyes of 66 patients who received the first dose of intravitreal anti-VEGF injection of 0.05 mL aflibercept or ranibizumab were recruited in this study. Of these 66 patients, 28 were Malay, 14 were Chinese, and 24 were Indian, with nine male patients, and 57 female patients were enrolled (Table I). The patients' ages ranged from 26 to 89 years old, with a mean (SD) age of 59.18 (12.06) years old. All these 66 patients were phakic. Diabetic macula oedema, wet age-related macular degeneration, and retina vein occlusion were found to be the most common pre-injection diagnosis (Table I).

Table I: Distribution of demographic data among study group. (n=66)

Characteristic	n (%)
Age (years)	59.18 (12.06)*
Sex	
Male	9 (12.5)
Female	57 (79.2)
Race	
Malay	28 (38.9)
Chinese	14 (19.4)
Indian	24 (33.3)
Laterality (n=72)	
Right eye	37 (51.4)
Left eye	35 (48.6)
Diagnosis (n=72)	
Clinical significant macula edema	52 (72.2)
Wet age related macula degeneration	10 (13/9)
Central retina vein occlusion with macula edema	5 (6.9)
Idiopathic polypoidal choroidal vasculopathy	3 (4.2)
Rupture microaneurysm	1 (1.4)
Ocular ischemic syndrome	1(1.4)

*Mean (SD)

Intraocular pressure parameters

Mean values of IOP at baseline, within 30 minutes and 1-hour post intravitreal injection of either ranibizumab or aflibercept were reported in Table II. Three groups of IOP comparison (baseline IOP – within 30 minutes post-injection, baseline IOP – 1-hour post-injection, and within 30 minutes post-injection to 1-hour post-injection) were analyzed using repeated-measures ANOVA, and the outcome was found statistically significant (Table III). At 1-hour post intravitreal injection, IOP was reduced to a safe level (<21mmHg) for majority patients except for four patients (4.44%). Among these 4 patients, one of them required IOP lowering agent as the IOP remained raised to 30mmHg at 1-hour post-injection, while one patient had IOP of 24mmHg and the remaining two patients had IOP of 22mmHg.

Anterior segment OCT parameters

Mean values of CACD, TIA500 nasal, TIA500 temporal, AOD500 nasal, and AOD500 temporal at baseline,

Table II: Mean values of IOP, CACD, TIA500 nasal, TIA500 temporal, AOD500 nasal and AOD500 temporal at baseline, within 30 minutes and 1-hour post intravitreal injection of 0.05ml aflibercept or ranibizumab. (n=72)

Parameters	Mean (SD)		
	Baseline IOP	Within 30 minutes post-injection	1-hour post-injection
IOP	16.54 (2.71)	22.71 (5.94)	17.81 (2.93)
CACD	2.77 (0.38)	2.77 (0.36)	2.78 (0.38)
TIA500 nasal	26.89 (8.26)	25.74 (9.11)	25.70 (8.15)
TIA500 temporal	28.32 (7.43)	26.66 (7.58)	26.87 (8.13)
AOD500 nasal	0.29 (0.10)	0.29 (0.10)	0.29 (0.10)
AOD500 temporal	0.30 (0.29)	0.30 (0.29)	0.30 (0.29)

Intraocular pressure (IOP); Central anterior chamber depth (CACD); Trabeculo-iris angle at 500 µm (TIA500); Angle opening distance at 500 µm (AOD500)

within 30 minutes and 1-hour post intravitreal injection of aflibercept or ranibizumab were summarized in Table II. Table III and IV describes the mean differences of CACD, TIA500 nasal, TIA500 temporal, AOD500 nasal, and AOD500 temporal at baseline, within 30 minutes and at 1-hour post intravitreal injection. Repeated-measures ANOVA showed statistically significant changes of temporal TIA500 between baseline with within 30 minutes and at 1-hour post intravitreal injection. The mean differences were 1.66 with P = 0.042 within 30 minutes and mean differences of 1.45 with the P = 0.041 at 1 hour respectively. However, there was no significant differences between other parameters.

Table III: The IOP and CACD changes using RMANOVA within group. (n=72)

Parameters	Mean Difference IOP (SD)	Mean difference (95% CI)		p-value
		Lower bound	Upper bound	
IOP changes				.
Baseline - 30 minutes	-6.17 (0.69)	-7.84	-4.491	<0.0001
Baseline - 1 hour	-1.26 (0.35)	-2.13	-0.40	0.002
30 minutes – 1 hour	4.90 (0.63)	3.36	6.45	<0.0001
CACD changes				
Baseline - 30 minutes	0.004 (0.01)	-0.02	0.03	>0.950
Baseline - 1 hour	-0.004 (0.01)	-0.03	0.02	>0.950
30 minutes – 1 hour	-0.008 (0.01)	-0.03	0.02	>0.950

Intraocular pressure (IOP); Standard deviation (SD); Confidence interval (CI); Central anterior chamber depth (CACD); Repeated measure ANOVA (RMANOVA)

Relationship of ocular biometry (ACD, TIA, AOD) changes with IOP changes from baseline to within 30 minutes, baseline to 1 hour, and within 30 minutes to 1-hour post intravitreal injection of anti-VEGF

Multiple linear regression was run to predict the IOP from the variables of CACD, TIA500 nasal, TIA500 temporal, AOD500 nasal, and AOD500 temporal within 30 minutes and 1-hour post intravitreal injection of anti-VEGF. Interestingly, these variables had statistically insignificant correlation, with the p-value of >0.05 for changes within 30 minutes and 1 hour after injection of intravitreal anti-VEGF (Table V).

DISCUSSION

Intravitreal anti-VEGF agents have been revolutionized and widely used in vitreoretinal and medical retinal practice all around the world in recent years. Although only small volume of 0.05ml of anti-VEGF agent was given, the increased of orbital fluid volume post

Table V: Relationship of ocular biometry (CACD, TIA500, AOD500) changes with IOP changes from baseline to 30 minutes and 30 minutes to 1 hour post intravitreal injection of anti-VEGF. (n=72)

Time	Factors	b (95% CI)	p-value
Baseline to 30 minutes	CACD	-2.22 (-6.07, 1.63)	0.254
	Nasal TIA500	-0.05 (-0.21, 0.10)	0.490
	Temporal TIA500	-0.07 (-0.25, 0.12)	0.475
	Nasal AOD500	-2.03 (-17.78, 12.73)	0.785
	Temporal AOD500	-8.06 (-21.22, 5.10)	0.225
30 minutes to 1 hour	CACD	-1.22 (-3.03, 0.59)	0.182
	Nasal TIA500	-0.05 (-0.13, 0.04)	0.259
	Temporal TIA500	-0.00 (-0.09, 0.09)	0.995
	Nasal AOD500	-2.51 (-9.86, 4.85)	0.499
	Temporal AOD500	-2.81 (-10.31, 4.68)	0.457

Confidence Interval (CI); Central anterior chamber depth (CACD); Trabeculo-iris angle at 500 µm (TIA500); Angle opening distance at 500 µm (AOD500)

Table IV: The nasal and temporal TIA500 and AOD500 changes using RMANOVA within group. (n=72)

Parameters	Nasal				Temporal			
	Mean Difference	Mean difference (95% CI)		*p-value*	Mean Difference	Mean difference (95% CI)		*p-value*
		Lower bound	Upper bound			Lower bound	Upper bound	
TIA500 changes								
Baseline - 30 minutes	1.15 (0.55)	-0.19	2.49	0.118	1.66 (0.66)	0.04	3.28	0.042
Baseline - 1 hour	0.70 (0.61)	-0.79	2.19	0.755	1.45 (0.57)	0.04	2.85	0.041
30 minutes- 1 hour	-0.45 (0.59)	-1.89	1.00	>0.950	-0.21 (0.56)	1.60	1.18	>0.950
AOD500 changes								
Baseline - 30 minutes	0.002 (0.01)	-0.016	0.020	>0.950	0.02 (0.01)	-0.003	0.035	0.128
Baseline - 1 hour	0.002 (0.01)	-0.018	0.022	>0.950	0.02 (0.01)	-0.002	0.040	0.091
30 minutes – 1 hour	0.000 (0.007)	-0.017	0.016	>0.950	0.003 (0.01)	-0.017	0.023	>0.950

Standard deviation (SD); Confidence interval (CI); Trabeculo-iris angle at 500 µm (TIA500); Angle opening distance at 500 µm (AOD500)

intravitreal injection causes significant changes in IOP, as shown in this study outcome. The acute rise in volume causes changes in intraocular fluid dynamics and anterior chamber morphology especially in the absence of reflux (14). However, the exact pathophysiology of sudden rise in IOP is still unknown, but the visual complication of untreated high IOP could be disastrous to patient and clinician.

In short, we observed the sudden short-term rise in IOP within 30 minutes but normalization of IOP in majority of patients at 1-hour interval post intravitreal injection in this study. Similar significant immediate changes of IOP were also reported by Gul Arikan et al. who studied on the outcome using different intravitreal anti-VEGF agents (triamcinolone acetonide and ranibizumab) with different dosage. Three groups of samples were recruited, with intravitreal injections of 0.1mL (4 mg) triamcinolone acetonide (TA, Group T4), 0.05 mL (2 mg) (TA, Group T2), and 0.05mL (0.5 mg) ranibizumab (Group R) given respectively. Of the total 229 eyes studied, a total of 51.9% sample (28 of 54 eyes) in Group T4, 31.9% (22 of 69 eyes) in Group T2 and 48.1% (51 of 106 eyes) in Group R reported to have immediate IOP increment of more than 25 mmHg post injection. While, 1.9% (one eye) in group T4, 2.9% (2 eyes) in group T2 and 1.9 % (2 eyes) in Group R remained to have high IOP of over 25mmHg at 30-minutes post injection (15).

A literature search and review of fourteen studies conducted by American Academy of Ophthalmology in Year 2018 also reported of immediate IOP elevation among all the patients who received intravitreal anti-VEGF injection (16). Coherent to our study, significant immediate raised of IOP within 30 minutes post intravitreal injection of anti-VEGF agent was reported, with reduction of initial IOP elevation to a safe level at 1 hour later.

This study also investigated the impact on anterior segment morphology within 30 minutes and at 1-hour post intravitreal injection, using the CACD, AOD500 (nasal and temporal) and TIA500 (nasal and temporal) parameter. All our patients were given intravitreal injection at the superotemporal quadrant of the par plana area using direct technique. There were no significant changes on ocular biometric parameter between baseline and post intravitreal injection was identified except for temporal TIA500 within 30 minutes and at 1-hour post-injection. We postulated that the changes in TIA500 temporal were probably contributed by route of anti-VEGF injected over temporal region. However, these changes did not contribute to the immediate rise of IOP post intravitreal injection as there is no significant relationship shown in statistical analysis.

Wen JC et al also demonstrated significant rise in IOP with changes on temporal AOD500, AOD750, and scleral spur angle in phakic eyes between pre and post intravitreal injection, but not on nasal angle morphology (17). These findings were similar to our study. Meanwhile, this study only involved small sample size with total of 21 eyes.

Another larger retrospective study conducted by Arslan GD et al. in Year 2019 involving 100 sample size reported no significant changes on IOP and central cornea thickness in all eyes but statistically significant small reduction in mean anterior chamber depth (ACD) and corneal endothelial cell density at one month after first and second intravitreal injections (p value of < 0.001 respectively) as compared to baseline reading. Meanwhile , no significant difference in the mean ACD in pseudophakic eyes (18). In short, single dose of intravitreal anti-VEGF injection would not affect IOP, and other ocular biometric parameters like CACD, iridocorneal angle, CCT, AOD, or sim K in short term period (10, 14, 18).

Few speculations in previous study. Some suggested that the inflammation in trabecular area causes direct raise in IOP (19). Some postulated direct damage to trabecular meshwork after multiple injection (20). On the other hand, there is also possibly of ranibizumab (48-kilodalton (kDa)) accumulated in trabecula and schlemm's canal causing direct or indirect obstruction of the outflow (19). These explained that anterior segment morphology does not correlate with IOP post injection as the changes is at molecular level that undetected using ASOCT.

Interestingly, some innovative manipulations such as scleral indentation with cotton swab and ocular digital massage pre- and post-procedure significantly reduces the excessive rise of IOP post intravitreal injection (20). The mechanism of this maneuver is yet to be elucidated. Besides, intravitreal injection techniques may also play a role in lowering down the spike of IOP rise. Tanwar S et. al demonstrated that higher intravitreal fluid reflux was seen with direct intravitreal injection technique, which inversely causing relatively lower transient rise of IOP as compared to oblique injection technique (21).

There are few limitations identified in our study. Firstly, two different anti-VEGF agents (ranibizumab and aflibercept) were used in this study depending to the underlying disease. However, both agents have different molecular weight and biochemical characteristic which may result in different outcome. Ranibizumab, a 48-kDa recombinant humanised immunoglobulin G1 kappa isotype antibody segment, binds to all VEGF-A isoform (22). While Aflibercept, a 115-kDa recombinant protein complex, works as competitive inhibitor of VEGF, binds to the Fc domain of immunoglobulin G1 (22) as well human VEGF-A, VEGF-B, and placental growth factor (23).

Besides that, the underlying pathologies in correlation to the IOP elevation post intravitreal injection was not

studied in this study as well. Meanwhile, Beak Su et. al reported no significant difference in IOP elevation between age related maculopathy and diabetic maculopathy post intravitreal injection of bevacizumab in their study conducted at The Republic of Korea (24). However, other pathologies such as central retina vein occlusion (CRVO) and ocular ischemic syndrome (OIS) might have different influence in the IOP as both CRVO and OIS has risk to get neovascular glaucoma (25, 26). Futher studies focusing on those high-risk population or specific pathology population may be a point of clinical interest. Current study also did not follow up and re-evaluate on the IOP level and ocular biometric changes among those patients with sustained IOP rise 1 hour post anti-VEGF injections. The total duration of normalization of IOP in this group of patients was not elicited in this study.

On the other hand, the use of anterior segment optical coherence tomography (AS-OCT) to evaluate ocular biometry changes provide us extra benefit in this study. It give an excellent quantitative and reproducible measurement of the anterior chamber angle (27). Visante OCT is widely used nowadays in daily practice setting as well as for in clinical study to detect any angle changes in response to intravitreal injections, cataract surgery, laser iridotomy in angle-closure glaucoma, and illumination alterations (14). All parameters were also evaluated by single well-trained operator to prevent inter-operator bias.

Besides, those patients with known underlying glaucoma, narrow-angle, high myopia, or any history of intraocular surgery were excluded in this study. In other words, any pre-existing ocular condition that predispose the patients to have a narrow angle post intravitreal injection had been rule out. Also, only patients with phakic eyes who receiving first intravitreal injection were being recruited in this study. This prevents accumulative factors that may contribute to high IOP and a narrow angle. Pseudophakic eyes were excluded in this study as this population was noted to have wider nasal and temporal anterior chamber angles, while age factor and initial IOP was found to have no confounding effects with anterior chamber angle (28).

CONCLUSION

In conclusion, intravitreal injection of anti-VEGF agents is associated with statistically significant short-term rise in IOP which normalized after 1 hour. No significant reduction in anterior chamber angle parameters other than temporal TIA post intravitreal injection was demonstratable. Thus, single dose of intravitreal anti-VEGF therapy is relatively safe, however, long term effects of the temporary rise in IOP need to be monitored and follow up with. Further study on at-risk population and repeated injections is needed to evaluate the risk and possible correlation with these complications.

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