Evaluation of Vitreous Reflux and Intraocular Pressure Changes in Repeated Intravitreal Injections

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ABSTRACT

Purpose: To evaluate effects of repeated intravitreal injections (IVIs) on vitreous reflux (VR) and intraocular pressure (IOP) changes in patients receiving intravitreal ranibizumab (IR) treatment.

Materials and Methods: We retrospectively reviewed files of patients with wet type age-related macular degeneration or diabetic macular edema patients treated with IR and demographic information0, lens status, IOP values, amount of VR and data regarding intravitreal treatment were recorded in all patients. The study included 74 eyes of 74 patients who had complete data in a least 2 IVI sessions. Data obtained during the first IVI session (IVI1), second IVI session (IVI2) and data from third IVE session in 14 of 74 patients were analyzed.

Results: In the study populations, there were 41 female (55.6%) and the mean age was 68.61 ± 9.81 (43-81) years. The mean number of IR injections was 4.89 ± 2.79 (1-10) and mean time was 7.1 ± 3.7 months (1-24 months) between IVI1 and IVI2. IOP values before and immediately after IVI were significantly higher in the IVI2 session, but there was no significant difference in IOP values on minute 30 after IVI (p: 0.032, <0.001, 0.518, respectively). The extent of IOP elevation after IVI was also significantly higher in IVI2 (p <0.001). The amount of VR was decreased in 44 patients (59.46%) whereas it was increased in 9 patients (12.16%) and no change was detected 21 patients (28.38%). There was no significant relationship between IOP changes after IVI and lens status, diagnosis, age and gender and (p> 0.05 for all data).

Conclusion: It was found that repeated IVI applications decreased the amount of VR and therefore increased the frequency of short-term IOP after IVI.

Keywords: Intraocular pressure, Intravitreal injection, Vitreous reflux.

INTRODUCTION

Intravitreal ranibizumab (IR) therapy is a frequently used treatment modality in many retinal diseases such as wet type age-related macular degeneration, diabetic macular edema (DME) and retinal vein occlusions.[1, 2] Majority of these disorders are chronic diseases, requiring repeated intravitreal injection (IVI) therapy.

Although IVI is a safe procedure in general, it is associated with risk for mild complications such as temporary inflammatory reaction or severe complications such as retinal detachment, vitreous hemorrhage or endophthalmitis.[3-6] In addition, acute intraocular pressure (IOP) elevations lasting 30-60 minutes are frequently seen after IVI and it has been suggested that repeated IVIs can cause IOP elevation at long-term after treatment.[6-12] In addition to these complications, vitreous reflux (VR) seen immediately after IVI and resultant subconjunctival bleb formation are observed in many patients.[13, 14] Although it is controversial whether VR carries additional risk for complication, it was found that there was a strict association between VR and IOP elevation after IVI.[6-9, 11, 14] The factors affecting IOP elevation after IVI and causes for VR decrease or increase have been investigated in many studies.[2, 5, 7-9, 11, 14, 15] Given that increasing number of patients with wet type age-related macular degeneration and DME and IVI therapies over time, the abnormalities that can result from repeated IVI therapies during IVI and at long-term after IVI should be investigated in a more detailed manner. For this purpose, we planned a retrospective study assessing patients underwent repeated IVI therapies in our clinic. In the present study, we aimed to investigate effects of repeated IVI ther-

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apies on VR and temporary IOP elevations by comparing amount of VR and IOP values during IVI applications at different times in the same patients receiving IR therapy.

MATERIALS AND METHODS

In the study, we assessed 74 eyes of 74 patients who received IR for DME or age-related macular degeneration at Ophthalmology Clinic between 1 March, 2015 and 1 March, 2019. The study was approved by Ethics Committee on Clinical Research (approval#2019/238; 21.11.2019).

In this retrospective study, we reviewed files of 530 patients who underwent more than one IR treatments during study period. The file review revealed that there were 316 cases in which IOP measurements before IVI (preIOP), immediately after IVI (postIOP) and on minute 30 after IVI (postIOP30) using Tonopen-Avial (Reichert Technologies, New York, USA) were recorded at patient files. Of these, 74 patients who fulfilled inclusion criteria and had VR records during IVI applications were included to the study. From patient files, data regarding IOP values, amount of VR, total number IR treatments, time from first IVI session to second IVI session and total number of IR treatments between first and second IVI sessions were extracted. The inclusion criteria were as follows: IOP<25 mmHg before IVI, no glaucoma or uveitis and no previous intraocular surgery other than uncomplicated phacoemulsification. Patients underwent intravitreal treatment other than IR, those with incomplete data and those without VR assessment were excluded.

In our clinic, IVI application was performed via direct injection technique through superior quadrant using 30 gauge needle (at 90° to sclera by targeting center of glob). Before the injection, the conjunctiva was properly mobilized with a sterile cotton swab to prevent vitreous from coming out of the conjunctiva. When active substance (0.05 cc) was injected, needle was pulled back without using any tamponade at conjunctiva by same angle. The amount of VR during procedure was recorded as "none", "small" or "great" by measuring conjunctival bleb diameter. The amount of VR was noted as "none" if no reflux was observed after IVI whereas "small" if bleb size was less than 3 mm and "great" if bled size was more than 3 mm.

All statistical analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). One way analysis of variance, paired sample t test and Wilcoxon test were used to assessed repeated measurements in a certain patient. In addition, correlations between variables were assessed by Pearson's correlation test for parametric data and by Spearman Rho correlation analysis for non-parametric data. A p value<0.05 was considered as statistically significant.

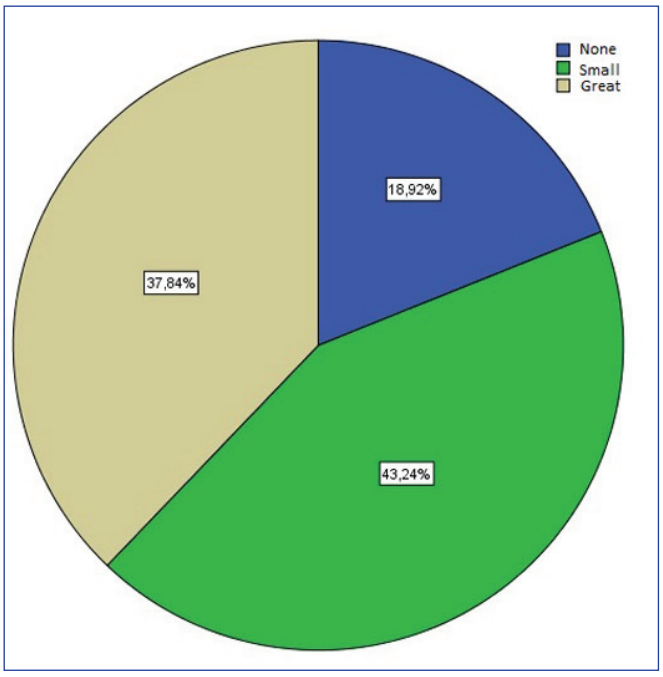
RESULTS

There were 33 male (44.6%) and 41 female (55.6%) in the study. Mean age was 68.61±9.81 years (43-81). Of the eyes included, 32 were right eyes while 42 were left eyes. Of 74 eyes, there were age-related macular degeneration in 43 (63.6%) and DME in 27 (36.5%). Twenty-one patients were pseudophakic. The mean duration was 7.1±3.7 months (1-24) and mean number of IR treatments was 4.89±2.79 (1-10) between IVI1 and IVI2. Table 1, Graphic 1 and Graphic 2 presents IOP values before and after IVI1 and IVI2, total number IVIs and amount VR. It was found that preIOP and postIOP values were significantly higher during IVI2 while there was no significant difference in postIOP30 values (p=0.032, p<0.001 and p=0.518, respec-

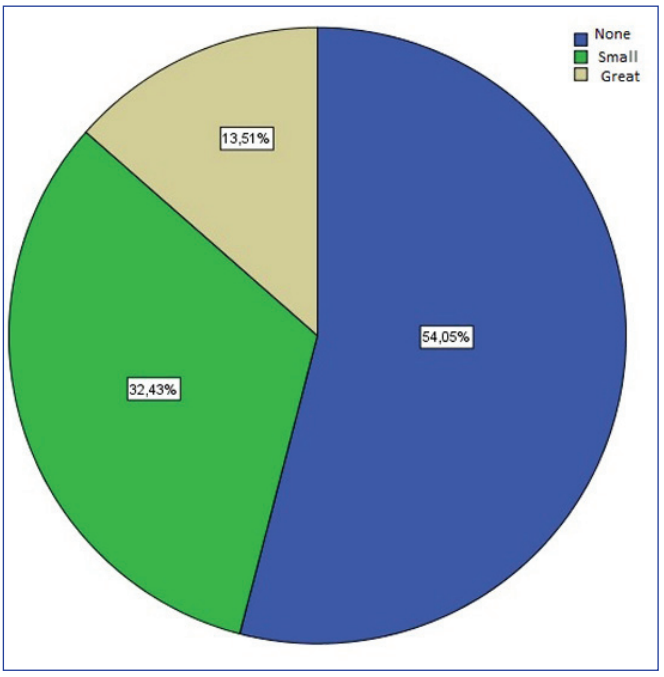
Table 1. *IOP levels, number of intravitreal injections and VR values at IVI1 and IVI2.*

Parameter	IVI1 (n=74)	IVI1(n=74)	p value
Total IVI count (n) ± SD	6.18 ± 3.65	11.07 ± 4.61	<0.001*
preIOP(mmHg) ± SD	15.29 ± 3.99	16.32 ± 3.96	0.032*
postIOP0 (mmHg) ± SD	30.38 ± 15.16	42.67 ± 14.44	<0.001*
postIOP30 (mmHg) ± SD	17.15 ± 6.01	17.51 ± 5.16	0.518*
postIOP - preIOP difference (mmHg) ± SD	15.06 ± 14.34	26.27 ± 13.95	<0.001*
postIOP30 - preIOP difference (mmHg) ± SD	2.01 ± 4.03	1.27 ± 4.69	0.213*
VR=none (n)	14	40	<0.001**
VR=mild (n)	32	24	
VR=high (n)	28	10	

IVI: Intravitreal injection, IVI: first IVI session, IVI2: subsequent IVI session, n: number of patients, postIOP: Intraocular pressure immediately after intravitreal injection, postIOP30: Intraocular pressure 30 minutes after intravitreal injection, preIOP: Intraocular pressure before intravitreal injection, SD: Standard deviation, VR: Vitreous reflux. * Paired sample t-test ** Wilcoxon test



Graphic 1. *VR status at first IVI session.*



Graphic 2. *VR status at second IVI session.*

Table 2: *Correlation between VR status and IOP levels at first and second IVI.*

Parameter	IVI1		IVI2	
	Correlation coefficient between VR and parameters*	p	Correlation coefficient between VR and parameters*	p
postIOP	-0.731	<0.001	-0.828	<0.001
postIOP30	-0.434	<0.001	-0.128	0.313
postIOP – preIOP difference	-0.728	<0.001	-0.792	<0.001
postIOP30 – preIOP difference	-0.541	<0.001	0.038	0.767

IVI: Intravitreal injection, IVI: first IVI session, IVI2: subsequent IVI session, postIOP: Intraocular pressure immediately after intravitreal injection, postIOP30: Intraocular pressure 30 minutes after intravitreal injection, preIOP: Intraocular pressure before intravitreal injection, VR: Vitreous reflux * Spearman's Rho correlation test

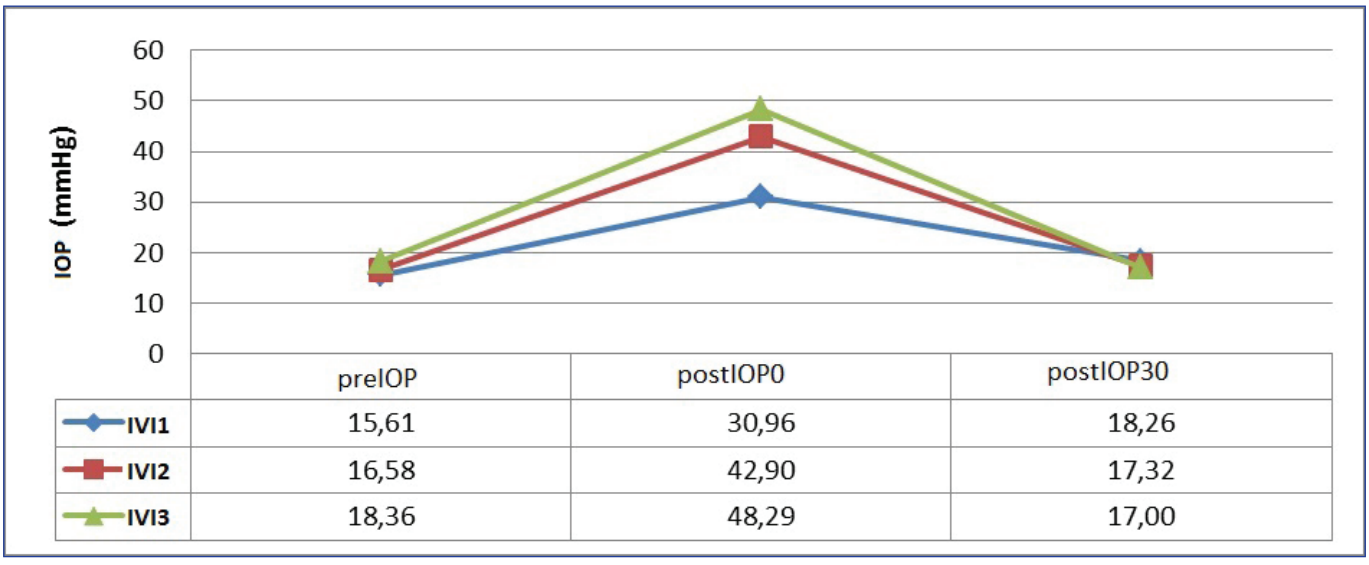
tively). The extent of IOP elevation after IVI was markedly higher during IVI2 (p<0.001). When assessed individually, there was a decrease in VR in 44 patients, an increase in 9 patients and no change in 21 patients. Bases on these data, it was found that there was a significant difference in VR between IVI1 and IVI2 with marked decrease in amount of VR during VR (p<0.001).

Of 74 patients included, it was found that only 14 patients had available data (VR, preIOP, postIOP, postIOP30 and number of IR) for third IVI session. Mean total number of IR treatments was 14.86±4.91 during IVI3 and mean number of IR treatments was 4.29±2.33 between IVI2 and IVI3. The amount of VR was "none" or "small" in 14 patients. The amount of VR was decreased in 8 patients while it was increased in one patient and remained unchanged in 5 patients. When repeated measurements were assessed, it was found that there was significant difference in IOP changes among 3 IVI sessions and that short-term IOP elevation was significantly higher during IVI3 (p<0.001). Graphic 3 presents IOP alterations after IVI sessions.

In correlation analysis, it was found that negative correlation between number of IR treatments and VR did not reach statistical significance at IVE1 while it became significant by increasing number of IR treatments at IVI2 (r=-0.66 and p=0.579 for IVI1 and r=-0.346 and p=0.003 for IVI2). There was no significant relationship between IOP changes after IVE and lens status, diagnosis, age and gender and (r value: 0.100.970; p> 0.05 for all data). It was found that there was a strong correlation between VR and IOP changes and postIOP values at both IVI1 and IVI2.

DISCUSSION

In our study, it was found that repeated IVIs led decrease in the amount of VR; thus, increase in the frequency of



	preIOP	postIOP0	postIOP30
IVI1	15,61	30,96	18,26
IVI2	16,58	42,90	17,32
IVI3	18,36	48,29	17,00

Graphic 3. *IOP values at IVI sessions.*

acute IOP elevation following IVI. Although preIOP values at IVI2 was found to be significantly higher, the study design limits drawing conclusion about effects of IVI on long-term IOP elevation. The short-term IOP elevation following IVI is generally considered as harmless; however, extremely high IOP levels carry risk for permanent loss of visual acuity and visual field in patients with glaucoma and those with problems in ocular micro-circulation. In our study, it was found that the risk is increased by repeated IVIs.

In many studies, it was shown that the extent of IOP elevation is higher following IVI in patients without VR during IVI. In previous studies, it was found that tunnel IVI technique and small needle diameter decrease VR and increase frequency of IOP elevation following IVI.[1, 5, 7, 11, 16, 17] Some authors suggested that short axial length is associated with IOP elevation following IVI.[9, 18] In conclusion, it has been reported that VR is primary cause for IOP elevation following IVI and that other factors do not comprise a significant risk for IOP elevation.[1, 5, 7, 11, 14, 16, 19] In studies on long-term risk and frequency of IOP elevation in patients undergoing intravitreal treatment, some authors reported that repeated IVI therapies lead prolonged IOP elevation.[6, 20] In these studies, it was found that number of IVI therapies, previous use of intravitreal steroid, IVI frequency less than 8 weeks, short axial length and presence of glaucoma increase risk for prolonged IOP.[6, 9, 21, 22] It has been proposed that IOP elevation may occur via several mechanisms including pharmacological effect of VEGF blockade, inflammation, impaired efflux of humor aqueous secondary to protein aggregation and trabecular injury due to recurrent IOP elevations.[12, 19] There are also studies proposing that IVI therapies do not increase risk for long-term IOP elevation or ocular hypertension.[23, 24] Although preIOP values were significantly higher at IVI2 when compared to IVI1, we could not draw conclusion whether there is an association between long-term IOP elevation following IVI and IVI therapies based on available data.

There are limited number of studies on how repeated or consecutive IVI therapies affect VR status and IOP elevations. In a study, Boon et al. reported that amount of VR was increased in 11 patients while it remained unchanged in 61 patients when a second IVI therapy was given 6 weeks after first IVI. Authors suggested that major determinants for amount VR are ocular characteristics such as detachment in posterior vitreous, degree of vitreous liquefaction, scleral thickness since amount of VR remained unchanged following second IVI session in majority of patients.[13] In other studies, it was observed that primary factors affecting amount of VR were IVI technique and needle size.[1, 5, 16, 17, 25] In addition, it was found that posterior vitreal detachment, age and number of total IVIs can be effective on amount of VR.[2, 13, 14, 19]

It was though that the decrease in amount of VR in our study was due to higher number of IVIs between first and second IVI sessions based on the study by Boon et al. [13] In addition, no significant relationship was detected between VR and lens status, diagnosis and age while it was seen that increasing number of IVIs in subsequent IVI session could decrease VR.

Our study has some limitations including the fact that majority of patients were assessed in 2 IVI sessions with limited number of patients underwent third session. Other limitations included retrospective design, lack of detailed assessment of VR status in all IVI sessions, VR character-

istics and their relationship with IOP. The strengths of our study included use of same agent by a single surgeon using same technique, classification of VR amount and comparison of same eyes over time.

In conclusion, it was found that repeated IVI applications decreased the amount of VR and therefore increased the frequency of short-term IOP after IVI. In particular, one should be more careful in IOP monitorization following IVI in patients with low visual potential or glaucoma/ocular hypertension requiring frequent IVI therapies. There is a need for further prospective studies assessing VR status and IOP alterations following each IVI session in patients requiring continuous IVI therapy due to age-related macular degeneration or DME.

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