Clinical Paper
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Reflux after intravitreal injection: an anterior segment optical coherence tomography study

Abstract

Purpose: To investigate the intraocular pressure and conjunctival thickness changes following the intravitreal injection

Methods: Sixty eyes of 60 patients having intravitreal injection for age-related macular degeneration, macular edema associated with diabetes, central retinal vein occlusion, and branch retinal vein occlusion were enrolled. Intraocular pressure (IOP) was measured by Tonopen-Avia (Reichert Inc., NY, USA) in sitting position and five superior-temporal conjunctival images were obtained using the Anterior Segment 5 Line Raster scanning protocol of Cirrus HD-OCT 4000 (Carl Zeiss Meditec, Dublin, CA, USA) just before the intravitreal injection. 0.05 ml bevacizumab with 27-gauge needle, 0.05 ml ranibizumab with 30-gauge needle, or dexamethasone implant with 23-gauge needle was injected into the vitreous cavity. The second IOP measurements and OCT measurements were taken within 5 mins of injection.

Results: The ranibizumab group included 25 subjects, the bevacizumab group included 23 subjects, and the dexamethasone group included 12 subjects. IOP increases following intravitreal injection were significantly higher in ranibizumab and bevacizumab groups compared with Dexamethasone implant group ($p<0.001$ and $p=0.007$, respectively). Although, the increase of conjunctival thickness following the intravitreal injection was highest in Dexamethasone implant group, the differences between the groups did not reach statistically significance ($p=0.153$).

Conclusion: A higher IOP elevation is observed if a small-gauge needle is used for intravitreal injection. The conjunctival thickness changes following the intravitreal injection did not differ between the groups.

Keywords: intravitreal injection, conjunctival thickness, retinal vein occlusion, IOP elevation

Volume 10 Issue 1 - 2020

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Received: January 11, 2020 | **Published:** February 07, 2020

Introduction

The intravitreal injection of various drugs is accepted as a safe intervention. Thus, use of antivascular endothelial growth factor (antiVEGF) and dexamethasone agents are used to treat several diseases of the posterior segment that are characterized by neovascularization or macular edema.[1,2] Optical coherence tomography (OCT) is a noninvasive imaging technique that widely accepted by clinicians to evaluate the retina and choroid.[3] Furthermore, various clinical applications of such as tear meniscus measurement, ocular surface disease (e.g., pterygium, pinguecula), Descemet's membrane detachment, corneal deposits (corneal dystrophies), keratitis, and glaucoma evaluation (angle assessment, morphological analysis of the filtering bleb after trabeculectomy).[4] To the best of our knowledge, no study has examined the amount of vitreous reflux using anterior segment OCT. The purpose of present study was to evaluate the conjounctival thickness changes related with the amount of vitreous reflux.

Methods

This prospective observational study was approved by the university Ethics Committee and was compliant with the tenets of Declaration of Helsinki. This work was supported by Research Fund of the Canakkale Onsekiz Mart University. (TSA-2015-568) Informed consent was obtained before the participation. Sixty eyes of sixty patient having intravitreal injection for aged related macular degeneration (AMD), central retinal vein occlusion (CRVO), and branch retinal vein occlusion (BRVO) were enrolled to the study. Patients with pre-existing glaucoma, spherical equivalent greater than 1.00 diopters were excluded. Eligible patients were assigned to one of the injection group regarding to type of drugs intravitreally administrated. All participants underwent ophthalmic examinations, including best-corrected visual acuity, refractive error, slit-lamp evaluation, and fundus examination. Intraocular pressure (IOP) was measured by Tonopen-Avia (Reichert Inc., NY, USA) in sitting position and five superior-temporal conjunctival images were obtained using the Anterior Segment 5 Line Raster scanning protocol of Cirrus HD-OCT 4000 (Carl Zeiss Meditec, Dublin, CA, USA) just before the intravitreal injection. All injections were performed under sterile condition by the same surgeon. Under topical anesthesia with %0.5 proparakain (Alcaine®, Alcon), periocular skins sterilized with 10 % povidone-iodine; after the eye was draped with plastic adhesive drape and a lid speculum was inserted, 5 % povidone-iodine were applied. 0.05 ml bevacizumab (Avastin; Genentech, San Francisco, CA) with 27-gauge needle, 0.05 ml ranibizumab (Lucentis; Novartis, Basel, Switzerland) with 30-gauge needle, or dexamethasone implant (Ozurdex, Allergan, Irvine, CA, USA) with 23-gauge needle was injected through the supero-temporal pars plana, 3.0-3.5 mm posterior of limbus into the vitreous cavity. Then, ophthalmic solution of moxifloxacin was administered. IOP measurements and OCT

measurements were taken within 5 mins of injection, respectively. Patients with vitreous reflux requiring any tamponade were excluded. Statistical analysis was performed using the SPSS version 20.0. Simple comparisons between groups were performed using the non-parametric Mann-Whitney U test, and comparisons between several groups were performed using the Kruskal-Wallis test.

Results

The ranibizumab group included 25 subjects (14 males) with a mean age of 63.24±10.50 (range, 43 to 82 years); the bevacizumab group included 23 subjects (12 males) with a mean age of 63.83±9.82 (range, 40 to 83 years); the dexamethasone group included 12 subjects (5 males) with a mean age of 63.75±12.04 (range, 37 to 79 years). The differences in age, gender, and lens status among the three groups were not statistically (p=0.838, 0.719, and 0.191, respectively) (Table 1). Diabetic macular edema was the most common reason for intravitreal injection in all the three groups (Table 1). IOP and conjunctival thickness measurements are shown in Table 2. Immediate postinjection IOP was compared among the groups, and it was found that Ranibizumab group had significantly higher postinjection IOP compared with Dexamethasone group (p<0.001). IOP increases following intravitreal injection were significantly higher in ranibizumab and bevacizumab groups compared with Dexamethasone implant group (p<0.001 and p=0.007, respectively). The serious complications such as endophthalmitis, retinal detachment, and vitreous hemorrhage, were not observed in any group. The numbers of patients with postinjection IOP values higher than 25 mmHg in Ranibizumab and Bevacizumab groups were eight (3.6 %) and five (2.2 %), respectively. These patients were treated using 500 mg of systemic oral acetazolamide. There was no patient with postinjection IOP value higher than 25 mmHg in Dexamethasone implant group. Conjunctival thickness changes did not reach the statistically significance between the groups (p=0.169).

Table 1 Demographics and ocular characteristics of patients

	Ranibizumab group	Bevacizumab group	Dexamethasone group	p
Age	63.24±10.50	63.83±9.82	63.75±12.04	0.838
Gender (male/female)	14-Nov	12-Nov	05-Jul	0.719
Lens status (phakic/pseudophakic)	Dec-13	17-Jun	07-May	0.191
Diagnosis				
Diabetic macular edema	18 (72.0%)	16 (69.6%)	8 (66.7 %)	
Age-related macular degeneration	5 (20.0 %)	2 (8.7 %)	3 (25.0 %)	
Central retinal vein occlusion	2 (8%)	4 (17.4 %)	1 (8.3 %)	
Branch retina vein occlusion	-	1 (4.3 %)	-	

Table 2 Intraocular pressure and conjunctival thickness measurements

	Ranibizumab group	Bevacizumab group	Dexamethasone group	p
Preinjection IOP, mmHg	16.20 ±3,20 (9,00-24,00)	15,96±4,52 (8,00-23,00)	15,58±3,26 (10,00-23,00)	0.538
Post injection IOP, mmHg	27,00±9,05* (15,00-49,00)	22,70±9,23 (8,00-49,00)	16,08±4,10* (8,00-23,00)	<0.001
IOP changes, mmHg	10.80±7,52* (2,00-30,00)	7,30±8,22¥ (-2,00-28,00)	0,50±2,75*¥ (-4.00 to 4,00)	<0.001
Preinjection conjunctival thickness, µm	249.04±65,51 (103,00-430,33)	258,03±46,30 (193,33-384,67)	259,39±52,73 (183,33-325,67)	0.903
Post injection conjunctival thickness, µm	345.63±91,17 (171,67-526,33)	381,09±96,63 (221,00-591,67)	408.36±93.56 (288,67-543.33)	0.169
Conjunctival thickness changes, µm	96.59±75,48 (-2,33-218,33)	123,06±78,73 (-11.67-274.00)	148,97±67,80 (54.34-257.33)	0.153

*p<0.001 Bonferroni corrected Mann–Whitney U test

¥p=0.007 Bonferroni corrected Mann–Whitney U test

Citation: Ersan I, Yildiz A. Reflux after intravitreal injection: an anterior segment optical coherence tomography study. *Adv Ophthalmol Vis Syst.* 2020;10(1):18–21. DOI: 10.15406/aovs.2020.10.00376

Discussion

Intravitreal drug injection is an effective route for retinal diseases. Also it allows the control of drug levels in the eye within a specified time. Physicians have a tendency to choose smaller gauge needles to decrease pain and injection related complications. The effect of injection technique related factors 55–10, axial length10, lens status6 on immediate IOP rise had extensively studied. Vitreous reflux was reported that the most important factor influencing the immediate postinjection IOP elevation.[5] Thus, injection techniques,[6] different needle sizes[7–15] were evaluated to decrease the vitreous reflux. Transient IOP increases following the anti-VEGF therapy have been studied extensively, whereas much is not known about the IOP increases following the DEX implantation. Previous studies concluded that the usage of smaller bore needles[5] and the lack of vitreous reflux[5] are related to higher immediate IOP spikes following the intravitreal injections. Pang et al.[5] reported immediate IOP increase was found to be significantly lower in eyes injected with 30-gauge needles compared with the smaller 32-gauge needles. Alagöz et al[16] showed none of the eyes showed an immediate IOP increase of ≥5mmHg in patients having intravitreal injection of dexamethasone implant. In accordance with the literature[17,18] we found that immediate IOP increases following intravitreal injection were significantly higher in ranibizumab using 30-gauge needle and bevacizumab groups using 27-gauge needle compared with Dexamethasone implant group ($p<0.001$ and $p=0.007$, respectively). We believe that higher IOPs in groups using smaller gauge needles were contributed by fewer vitreous reflux in smaller gauge needles.[19]

Various degrees of postinjection reflux is occasionally seen due to the intravitreal drug injection[11] It was demonstrated that the reflux contains not only vitreous but also injected intravitreal drug1912 The reflux of injected drug raises the concerns of loss of therapeutic dose. To address these concerns Brodie et al.[20] studied on cadaveric human eyes and reported the average loss of the original 50-µL injection was only 0.74%, with a maximum loss of 4.30%. Using digital image analysis system in porcine eyes, the reflux contained some of the injected material but was predominantly composed of vitreous[21] There was a higher incidence of postinjection reflux in eyes injected with 30-gauge (53%) compared with those injected with 32-gauge (13%, $P=0.0007$).[5]

Reflux was evaluated with the observation of presence or absence of conjunctival bleb formation, digital photographic technique,[20] colorimetric comparison in enucleated bovine eyes,[8,22,23] positron emission and computed tomography,[24] cotton swab test[25] measuring the conjunctival bleb diameter To the best of our knowledge, no study using anterior segment OCT has examined the subconjunctival blep due to the postinjection reflux. In accordance with the studies that reported a smaller needle bore size results in lower occurrence of vitreous reflux, we found a tendency of increasing conjunctival thickness changes with increasing the needle size, but the difference between the groups did not reach the clinically significance ($p=0.153$).[26–28] The limitations of this study is the small sample size, and the various variables that could not be controlled including status of vitreous, and the number of previous injections. One more limitation of the study is that only the conjunctival thickness measurements are used to indicate the amount of VR. Based on these results, we advise to take into account the immediate IOP increase in patient with a small amount of vitreous reflux. Future studies concerning advantages and disadvantages of using smaller gauge needles for intravitreal injection should be carried out as the physicians have tendency to favor smaller gauge needles.

Acknowledgments

This prospective study was supported by Research Fund of the Canakkale Onsekiz Mart University. (TSA-2015-568).

Conflicts of interest

Author declares that there is no conflict of interest.

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Citation: Ersan I, Yildiz A. Reflux after intravitreal injection: an anterior segment optical coherence tomography study. *Adv Ophthalmol Vis Syst.* 2020;10(1):18–21. DOI: 10.15406/aovs.2020.10.00376