Alterations in Anterior Segment Parameters After Intravitreal Anti-VEGF Injection Assessed by Scheimpflug Camera

İntravitreal Anti-VEGF Enjeksiyonu Sonrası Ön Segment Parametrelerinde Scheimpflug Camera ile Saptanan Değişimler

Selçuk KARA[1], Hasan Ali TUFAN[2], Baran GENCER[1], Sedat ARIKAN[1], Ahmet Murat HONDUR[3], İsmail ERŞAN[1]

ABSTRACT

Purpose: To determine the short-term intraocular pressure (IOP) and anterior segment alterations following intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF).

Materials and Methods: A prospective series of consecutive patients undergoing injection of 0.05 mL intravitreal bevacizumab or ranibizumab, without vitreous reflux, was investigated. IOP measurements were performed using Tono-Pen. Anterior segment parameters including anterior chamber depth (ACD), anterior chamber volume (ACV) and anterior chamber angle (ACA) were measured with the Sirius Scheimpflug camera. Measurements were obtained in each eye just before the injection, 5 minutes after the injection and 24 hours after the injection.

Results: A total of 42 eligible patients were included in this study. Mean baseline IOP was 15.9±3 mmHg and it increased to 25.9±10.5 mmHg 5 minutes after the injection ($p<0.001$). 24 hours after the injection, IOP normalized with a value of 15±3.4 mmHg ($p>0.05$). Compared with baseline, changes in ACD and ACV were statistically non-significant at each time-point ($p>0.05$). The mean ACA decreased from 38±6.7° at baseline to 36.7±7.1° five minutes after injection ($p=0.004$). Mean ACA value normalized at 24 hours with a value of 37.6±7.1° ($p>0.05$).

Conclusion: Anterior segment parameters, except ACA, seem to be unchanged after intravitreal injection. The alterations in ACA returned to normal values with the decrease of IOP values after 24 hours of injection.

Key Words: Intravitreal injection; intraocular pressure; anterior chamber depth; anterior chamber volume; anterior chamber angle.

ÖZ

Amaç: Anti-vasküler endotelyal growth factor (Anti-VEGF) enjeksiyonu sonrası kısa dönem göz içi basıncı (GİB) ve ön segment değişimlerini belirlemek.

Gereç ve Yöntem: Vitreus reflüsü olmadan 0.05 ml intravitreal bevacizumab veya ranibizumab enjeksiyonu yapılan prospektif sıralı hasta serisi incelendi. GİB ölçümleri Tono-Pen ile yapıldı. Ön kamara derinliği (ÖKD), ön kamara hacmi (ÖKH) ve ön kamara açısını (ÖKA) içeren ön segment parametreleri Sirius Scheimpflug camera ile ölçüldü. Ölçümler enjeksiyondan hemen önce, enjeksiyondan 5 dakika sonra ve enjeksiyondan 24 saat sonra alındı.

Bulgular: Bu çalışmaya uygun toplam 42 hasta dahil edildi. Başlangıç ortalama GİB 15.9±3 mmHg idi ve enjeksiyondan 5 dakika sonra 25.9±10.5 mmHg'ye yükseldi ($p<0.001$). Enjeksiyondan 24 saat sonra GİB 15±3.4 mmHg olarak normale döndü ($p>0.05$). Başlangıç ile karşılaştırıldığında herbir zaman diliminde ÖKD ve ÖKH istatistiksel olarak anlamlı değildi ($p>0.05$). Ortalama ÖKA, başlangıçta 38±6.7°'den enjeksiyondan 5 dakika sonra 36.7±7.1°'e düştü ($p=0.004$). 24 saat sonra ortalama ÖKA değeri 37.6±7.1° olarak normale döndü ($p>0.05$).

Tartışma: İntravitreal enjeksiyon sonrası ön segment parametrelerinin, ÖKA hariç değişmediği görülmektedir. ÖKA'daki değişimler enjeksiyondan 24 saat sonra GİB değerlerinin düşmesiyle normale döndü.

Anahtar Kelimeler: İntravitreal enjeksiyon; göz içi basıncı; ön kamara derinliği; ön kamara hacmi; ön kamara açısı.

Key Words: Brinzolamide/timolol maleat, dorzolamide/timolol maleat, intraocular pressure, glaucoma.

1- M.D. Asistant Professor, Canakkale Onsekiz Mart University, School of Medicine, Department of Ophthalmology, Canakkale/TURKEY
KARA S., selckara@gmail.com
GENCER B., barangencer@gmail.com
ARIKAN S., drsarikan@gmail.com
ERSAN I., isersan@gmail.com

2- M.D. Associate Professor, Canakkale Onsekiz Mart University, School of Medicine, Department of Ophthalmology, Canakkale/TURKEY
TUFAN H.A., ha_tufan@hotmail.com

3- M.D. Associate Professor, Gazi University, School of Medicine, Department of Ophthalmology, Ankara/TURKEY
HONDUR A.M., ahondur@yahoo.com

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Yazışma Adresi / Correspondence Adress: M.D. Asistant Professor, Selcuk KARA
Canakkale Onsekiz Mart University, School of Medicine, Department of Ophthalmology, Canakkale/TURKEY

Phone: +90 532 780 02 83
E-mail: selckara@gmail.com

INTRODUCTION

Antiangiogenic agents targeting vascular endothelial growth factor (VEGF) have been widely accepted for the treatment of ocular neovascular diseases, such as age-related macular degeneration (AMD), diabetic retinopathy (DRP) and retinal veno-occlusive diseases (RVOD).[1] Current research has focused on bevacizumab (Avastin, Genentech, San Francisco, CA, USA) which is a recombinant humanized full-length monoclonal anti-VEGF antibody and ranibizumab (Lucentis, Genentech, San Francisco, CA, USA), a fragment of this anti-VEGF antibody.

Although the safety and efficacy of intravitreal ranibizumab or bevacizumab injection in many retinal disorders is well-established in the literature, these may cause ocular adverse effects.[2,3] There is a general consensus that ocular complications following intravitreal injections are more likely caused by the injection rather than the administered agent. An established side effect recurring in all intravitreal injections is transient intraocular pressure (IOP) elevation.[4,5] Such an event could be expected as a consequence of increased vitreous volume, which depends on the injection procedure (the volume of injected agent, the amount of reflux after injection) and ocular variables (axial length, scleral rigidity, vitreous structure).[6] Sustained IOP elevation following intravitreal anti-VEGF injection has also been described in previous studies with a prevalence of 3.45% to 9.9%.[7,8] Several potential mechanisms have been suggested including toxic effect of anti-VEGF agents on anterior segment structures, chronic inflammation related to repeated injections, mechanical obstructions of outflow pathways either by the administered drug or silicone oil droplets derived from the syringe.[9-11] However, the underlying pathophysiology in these cases is still puzzling as most of these suggestions have not been proven yet.

IOP and ocular axial length changes following intravitreal anti-VEGF injection have been meticulously studied.[12,13] However, alterations in anterior segment parameters including anterior chamber depth (ACD), anterior chamber angle (ACA) and anterior chamber volume (ACV) following intravitreal anti-VEGF injection have been evaluated only in a few studies and ACA were measured by anterior segment optical coherence tomography.[13-15]

Advances in anterior segment imaging such as the Scheimpflug camera have allowed quantitative and reproducible measurements of anterior segment parameters.[16,17] This device contains a rotating Scheimpflug camera and a Placido-disk topography and allows full analysis of the anterior segment from the anterior corneal surface to the posterior lens surface. Evaluation of anterior segment parameters may improve our understanding about IOP elevation following intravitreal injections and its consequences. The purpose of this study was to investigate the IOP and anterior segment (ACD, ACV and ACA) alterations by the Scheimpflug camera after intravitreal anti-VEGF injections.

MATERIAL AND METHODS

This was a prospective case series of consecutive patients who underwent intravitreal bevacizumab or ranibizumab injection at our clinic for the treatment of AMD, DRP and RVOD. The study adhered to the tenets of the Declaration of Helsinki and was approved by the local ethics committee of Canakkale Onsekiz Mart University. A consent form was obtained from all participants before enrolment and only one eye of each patient was evaluated. All patients underwent a complete ophthalmologic examination including slit lamp biomicroscopy, tonometry, gonioscopy and fundoscopy. Patients with glaucoma, pseudoexfoliation syndrome, any other ocular or retinal pathologies, any previous ocular trauma or surgery, previous treatment with laser trabeculoplasty or iridotomy and patients who were unable/reluctant to give informed consent were excluded. Patients who had subconjunctival reflux following injection were also excluded.

All injections were performed by the same physician (HAT) with a uniform protocol in the operating room. All patients were positioned supine for the injection and a topical anaesthetic (oxybuprocaine) was administered. 10% povidone iodine was used to disinfect the ocular surface. A sterile drape and a lid speculum were applied, and then povidone iodine 5% was instilled into the conjunctival sac. A 0.05 mL volume of bevacizumab or ranibizumab was injected with 30-gauge needles after marking the injection site 3.5 mm away from the limbus. The injection site was massaged with a sterile cotton swab immediately after the needle was withdrawn and the surgeon inspected the eye for subconjunctival reflux. Positive detection of hand motion was tested in all cases.

Three measurements of IOP were performed with the Tono-Pen (Tono-Pen AVIA® Applanation Tonometer, Reichert Technologies, USA) just before the lid speculum was applied (IOP0), just after the lid speculum was removed (IOP1) and 24 hours after the injection (IOP2). Anterior segment parameters including ACD, ACV and ACA were measured with the Sirius Scheimpflug camera (Costruzione Strumenti Oftalmici, Florence, Italy). All measurements were performed in a room with a standard dim illumination by the same trained examiner. Three measurements were obtained in each eye just before the injection, 5 minutes after the injection and 24 hours after the injection, and the best image was used in quantitative analysis. The ACV, ACD and ACA measurements were calculated automatically by the software. The ACA used in this study was an average of the superior, inferior, nasal and temporal angles.

Statistical tests were performed with the SPSS software version 16.0 (SPSS Inc, Chicago, Illinois, USA). A Paired samples t-test was performed to compare GİB, ACV, ACD and ACA values of eyes just before the injection, 5 minutes after the injection and 24 hours after the injection and, in cases of deviation from normal distribution, the non-parametric Wilcoxon signed rank test was used. Pearson and Spearman correlation coefficients were used to evaluate potential relations between IOP and anterior chamber parameters. P values less than 0.05 were considered statistically significant. The parameters were presented as mean±standard deviation.

RESULTS

A total of 96 patients received ranibizumab or bevacizumab injections during the study period (January-April 2013). Forty two of these patients were eligible according to the inclusion criteria of this study and were included. Twenty nine (69%) patients were male, and the mean age was 64±10.4 years. The indications for intravitreal injection were AMD in 24 (57%) patients, DRP in 15 (36%) patients and RVOD in 3 (7%) patients.

IOP and anterior segment alterations are summarized in Table. Mean baseline IOP before the injection (IOP0) was 15.9±3 mmHg and it increased to 25.9±10.5 mmHg just after the injection (IOP1), (p<0.001). 24 hours after the injection (IOP2) IOP normalized with a value of 15±3.4 mmHg (p>0.05). Compared with the pre-injection measurements, changes in ACD were statistically non-significant (p>0.05) at each time-point. Similarly, mean ACV did not change significantly at any time point. At 5 minutes after the injection, Mean ACA significantly decreased from 38±6.7 at baseline to 36.7±7.1 (p=0.004). Mean ACA normalized at 24 hours. There was no correlation between IOP and ACA.

DISCUSSION

Numerous reports highlight the transient or sustained IOP elevation following intravitreal anti-VEGF injections.[8,18,19] While short-term IOP elevation may be explained with the increased vitreous volume following the introduction of additional fluid into the vitreous cavity, exact mechanism of long-term IOP elevation is still not obvious. IOP monitoring after injection is a contraversial issue, some studies recommend IOP checking after intravitreal injection whereas others not.[20-22]

In agreement with previous studies, an acute rise in IOP immediately after intravitreal injection was observed in our study.[18,19] None of our patients had pre-existing glaucoma or previous cataract surgery, which potentially can lead to IOP elevation and affect anterior chamber measurements. Some authors have postulated that recurrent injections may lead anterior segment inflammation resulting in IOP elevation.[10,23] IOP is one of the mechanical factors that may affect ocular structures directly.[24] Animal and human studies have demonstrated that elevation in IOP is associated with scleral stress and creep, resulting in axial elongation.[25,26] However, the effect of additional vitreous volume on anterior segment parameters is not well-clarified in the literature. The main focus of the current study was the anterior chamber changes following intravitreal anti-VEGF agents. We used a Scheimpflug-based imaging device (Sirius) to evaluate ACD, ACV and ACA. This device permits evaluation of anterior segment structures from the anterior corneal surface to the posterior lens surface with a good repeatability.[16,17] We did not find any significant change in ACV measurements at any time point and there was a decrease in ACD at 5 minutes after injection but not significant (p=0.05). Goktas et al.[13] observed a transient IOP elevation without any alteration in axial length and ACD after the intravitreal injection of 0.05 ml ranibizumab, confirming our results. They concluded that increase in IOP after the injection seemed to be irrelevant to axial length and ACD. Kerimoglu et al.,[14] evaluated ACD and ACV changes after 0.1 ml intravitreal triamcinolone acetonide injection. They found a decrease in both ACD and ACV at 5 minutes after injection, and these values returned to normal values at 15 minutes after injection. However, they have administered twice the volume used in our study.

The most striking finding of our study was the significant narrowing of the ACA at 5 minutes after injection, which returned to normal at 24 hours. Alkin et al.,[15] evaluated the effects of Intravitreal injection of bevacizumab (0.05 ml) or bevacizumab-triamcinolone combination (0.1 ml) on anterior segment morphology and they didn't find any statistically significant difference from baseline in ACA at 5 minutes and the other time points. This contrary

Table: *Values of IOP and anterior segment parameters.*

	Baseline	5 min after injection	24 h after injection
IOP (mmHg)	15.9±3	*25.9±10.5	15.05±3.4
ACD (mm)	2.55±0.3	2.52±0.3	2.55±0.3
ACV (mm3)	127.5±26.6	134.2±43.5	149.3±19.3
ACA (degree)	38±6.7	*36.1±7.1	37.6±7.1

IOP; Intraocular Pressure, ACD; Anterior Chamber Depth, ACV; Anterior Chamber Volume, ACA; Anterior Chamber Angle.

*p<0.05

finding in ACA may be related with liquefaction of vitreus which facilitates water displacement between vitreus compartments. Additional vitreous volume, if there was no loss of fluid from any of the compartments, would increase the pressure differences between posterior globe (higher) and the anterior chamber. Furthermore, rapidly increased vitreous volume would move forward, carrying the iris and lens with it, resulting in narrowing of the anterior chamber. However, if water freely passed through the vitreous without any resistance, the volume increase posteriorly would be accommodated by aqueous outflow through the trabecular meshwork, eventually. In this study, although there was statistically significant reduction in ACA five minutes after the injection without a simultaneous change in ACV or ACD, the change was almost significant (p=0.05) in ACD. Also it is suggested that ACV is a less sensitive marker of changes in the anterior chamber than ACA.

Our study may be limited by its relatively small sample size. Another limitation may be the evaluation of these parameters at only three different time points. Thus, we are unable to come to a conclusion about the time-dependent alterations of anterior segment parameters following intravitreal injection. In addition, ACA imaging with Scheimpflug camera might cause measurement errors due to light-scattering at the angle. Further refinements in instrumentation may overcome such limitations.

In conclusion, anterior segment parameters, except for ACA, seem to be stationary after intravitreal injection. The evaluation of these parameters may be important, particularly in patients with narrow angle. Alterations in anterior segment parameters following intravitreal injections may be worth to investigate further, as it may provide predictive values regarding the potential IOP elevation and ACA shallowing effect of intravitreal injections.

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