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ORIGINAL PAPER

The early effects of intravitreal anti vascular endothelial growth factor agents on intraocular pressure and central corneal thickness

Esra Omay · Ufuk Elgin · Emine Sen · Pelin Yilmazbas

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Abstract 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 ± 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 1st, 7th, and 30th 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.

Keywords Bevacizumab · Ranibizumab · Anti-VEGF · Intravitreal injection · Intraocular pressure · Central corneal thickness

Introduction

Intravitreal injection (IV) of anti-VEGF agents are increasingly used for the treatment of retinal vascular diseases [1–4]. Bevacizumab (Avastin™, Genentech, Inc., South San Francisco, CA, and Roche, Basel, Switzerland) and ranibizumab (Lucentis™, Genentech, Inc., South San Francisco, CA, and Novartis Pharma AG, Basel, Switzerland) are the most

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E. Omay (✉) · U. Elgin · E. Sen · P. Yilmazbas
Ulucanlar Eye Research Hospital, Ulucanlar Caddesi No: 59, Altindag, 06240 Ankara, Turkey
e-mail: aesrakaraagac@gmail.com

frequently used anti-VEGF agents in ophthalmology and which are both antibodies to VEGF [5]. Ranibizumab was approved by the Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products for the treatment of ARMD while bevacizumab is off-label but widely used because of its low price [5].

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 [6–8]. Intraocular pressure (IOP) elevation is the most frequent ocular complication and it is generally transient; however, there are rare cases who need medical or surgical anti-glaucoma treatment [9, 10]. Generally a transient elevation occurs because of the given volume of anti-VEGF agent after injection [11–15].

One of the factors affecting central corneal thickness regardless of corneal endothelial cell density is the high intraocular pressure, due to gradient. In a recent study, the central corneal thickness before and at 7 days and 6 months after the first intravitreal ranibizumab injection was measured and there was no significant difference [16].

In this study, our aim was to investigate the early effects of IV injection of two anti-VEGF agents, bevacizumab and ranibizumab, on IOP and whether there is a relationship between the central corneal thickness (CCT) with sudden intraocular pressure changes, over time in the first month after injection, in non-glaucomatous cases.

Materials and methods

One hundred and nine eyes of 109 adult cases, who had IV bevacizumab (Avastin™, Genentech, Inc., South San Francisco, CA, and Roche, Basel, Switzerland) and ranibizumab (Lucentis™, Genentech, Inc., South San Francisco, CA, and Novartis Pharma AG, Basel, Switzerland) injections because of age-related macular degeneration (ARMD), retinal venous occlusion (RVO), diabetic retinopathy, and macular edema or central serous chorioretinopathy (CSCR) between January 2014 and June 2014 at Ulucanlar Eye Research Hospital, were included to our prospective study, consecutively. All of the study procedures were conducted in accordance with the Declaration of Helsinki and informed consents were taken from all of the participants. This study was approved by The Ethical Committee of Numune Training and Research Hospital, Ankara, Turkey.

Adult cases older than 18-year old with exudative ARMD, macular edema and/or retinal neovascularization due to the central or branch RVO, and macular edema and/or retinal neovascularization due to DM and CSCR were included to the study. We excluded the cases who were younger than 18-year old, who had any type of glaucoma or IOP increase before, who had pseudoexfoliation syndrome, aphakia, any other corneal diseases those might affect corneal thickness, the cases with medical histories of any ocular trauma, surgeries other than uncomplicated phacoemulsification and posterior chamber intraocular lens implantation at least 6 months ago, corticosteroid use, contact lens use, chronic inflammation, and IV injection of any agents before.

Before the injections, all of the cases had a detailed ophthalmologic examination including best-corrected visual acuities with Snellen charts, anterior and posterior segment examinations, fluorescein angiography, optical coherence tomography (Spectralis, Heidelberg engineering, Germany), IOP measurements with non-contact tonometer (Canon TX-20 Full Auto Tonometer, Canon medical systems, USA) and CCT measurements by ultrasonic pachymeter (UP-1000 Ultrasonic Pachymeter Nidec). We used non-contact tonometer because of its ease of use, non-contact, and non-irritating characteristic in recent post-injection cases. 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. The measurements, both IOP and CCT, at follow-up visits were carried out roughly at the same time as baseline (between 10.00 am and 12.00 pm) to avoid diurnal physiological changes. The IOP and CCT measurements were taken at least three times at one time point and the final IOP and CCT were calculated as mean of those.

Surgical technique

All the injections were performed in the operating room. After topical (Alcaine 0.5 % Ophthalmic Solution Alcon) anesthesia, disinfection of the ocular surface with povidone iodine and covering with ophthalmic surgical drape, bevacizumab (1.25 mg/0.05 ml), or ranibizumab (0.5 mg/0.05 ml) was

injected intravitreally 3.5 mm from the limbus by using a 30-gauge needle in the inferotemporal quadrant. The injection site was occluded with a cotton tip for about 1 min. Topical moxifloxacin hydrochloride 4 × 1 (Vigamox® 0.5 % Ophthalmic Solution Alcon) was used postoperatively for 3 days.

Statistical analysis

All statistical analyses of the study were performed using SPSS for Windows (SPSS Inc., Chicago, IL, USA) software. Paired sample *t* tests were used for the analysis, and the level of significance was set at <0.05. Multiple testing with general linear model was done for correction and confirmation of data.

Results

The demographic characteristics, diagnosis, and the status of the lens are described in Table 1 for each anti-VEGF agents separately and in total. All patients were Turkish Caucasians.

The values of IOP for bevacizumab and ranibizumab before and after injection are summarized in Table 2. The IOP increased significantly 30 min after the injection for both bevacizumab and ranibizumab (paired sample t test, $p = 0.0001$ and $p = 0.007$, respectively). Significant decreases were observed at the 1st, 7th, and 30th day after bevacizumab injection (paired sample t test, $p < 0.001$). There was also significant decrease in IOP at 7th day (paired sample t test, $p = 0.008$); however, there was no significant decrease in IOP at 1st and 30th day (paired sample t test, $p = 0.072$ and 0.934, respectively) after ranibizumab injection (Table 2).

The values of baseline, post-injection 7th day and post-injection 1st month CCT values, are 542.12 ± 37.57 μm, 542.26 ± 36.51 μm and 541.41 ± 35.97 μm, respectively. 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).

Discussion

The IV use of anti-VEGF agents can be associated with elevation in IOP and rarely glaucoma though the exact mechanism is not completely clear [9, 10].

Table 1 The demographic characteristics and the diagnosis of the cases

	Bevacizumab (97 cases)	Ranibizumab (12 cases)	Total (109 cases)
Mean age ± SD	62.76 ± 10.86	70.17 ± 10.64	63.58 ± 11.04 (29–86 years)
(range)	(29–86 years)	(40–81 years)	
Sex (n/%)			
Male	48/49.5 %	8/66.7 %	56/51.4 %
Female	49/50.5 %	4/33.3 %	53/48.6 %
Diagnosis (n/%)			
Diabetic retinopathy	54/55.7 %	2/26.7 %	56/51.4 %
ARMD	24/24.7 %	9/75 %	33/30.3 %
RVO	11/11.3 %	–	11/10.1 %
CSCR	8/8.3 %	1/8.3 %	9/8.3 %
Side of the eye (n/%)			
Right	41/42.3 %	7/58.3 %	48/44 %
Left	56/57.7 %	5/41.7 %	61/56 %
Status of the lens (n/%)			
Pseudophakic eye	65/67 %	6/50 %	71/65.1 %
Phakic eye	32/33 %	6/50 %	38/34.9 %[a]

ARMD age-related macular degeneration, *RVO* retinal venous occlusion, *CSCR* central serous choroidal retinopathy

[a] All thirty eight patients had undergone uncomplicated phacoemulsification and posterior chamber intraocular lens implantation at least 6 months before the injection

Table 2 The values of intraocular pressure before and after the injection and the differences between the pre-injection and post-injection values

	IOP (mean ± SD) (mmHg)	The difference from basal IOP (mmHg)	*P* value*
Total			
Baseline IOP	16.48 ± 4.39		
30 min	22.02 ± 7.60	+ 5.54 ± 7.87	0.0001
1st day	14.09 ± 4.42	−2.38 ± 4.36	0.0001
7th day	14.21 ± 4.24	−2.26 ± 3.84	0.0001
1st month	15.06 ± 4.62	−1.42 ± 4.11	0.0001
Bevacizumab			
Baseline IOP	16.77 ± 4.47		
30 min	21.81 ± 7.27	+ 5.04 ± 7.47	0.0001
1st day	14.32 ± 4.58	−2.45 ± 4.49	0.0001
7th day	14.49 ± 4.31	−2.27 ± 4.00	0.0001
1st month	15.19 ± 4.68	−1.59 ± 4.18	0.0001
Ranibizumab			
Baseline IOP	14.08 ± 2.77		
30 min	23.67 ± 10.12	+9.58 ± 10.09	0.007
1st day	12.25 ± 2.13	−1.83 ± 3.18	0.072
7th day	11.92 ± 2.74	−2.16 ± 2.33	0.008
1st month	14.00 ± 4.15	−0.08 ± 3.42	0.934

IOP intraocular pressure

* Paired sample *t* test, confirmed with general linear model

However, it is thought to be related with inflammation. As ranibizumab and bevacizumab are antibodies, they have crystallizable fragment (Fc) portion which might bind immune molecules such as complement factors and trigger an immune response [17]. Also some other mechanisms like the passage of high-molecular-weight proteins into the anterior chamber via disrupted anterior hyaloid or disrupted zonules and the accumulation of anti-VEGF agents in the trabecula might play a role [18, 19].

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 [11–15]. In our study, we aimed to investigate the effects of intravitreally injected anti-VEGF agents on IOP and CCT within the post-injection first month in the cases with initial injections. We excluded the cases with neovascular glaucoma (NVG) and other types of glaucoma in order to eliminate the effect of glaucoma on IOP values.

Immediate raise in IOP is frequently seen after the IV anti-VEGF injections like other pharmacological agents. Lemos-Reis et al. measured the IOP values of 291 cases immediately before and after injection of single bevacizumab intravitreal injection in a seated position by Icare® tonometer in their study [12]. They observed IOP increase more than 50 mmHg in about one third of patients. Bakri et al. investigated the changes in IOP after IV injections of 0.1 ml triamcinolone, 0.09 ml pegaptanib, and 0.05 ml bevacizumab in their 221 cases within the 30 min after the injection [13]. Only 3 cases treated by triamcinolone needed anti-glaucomatous therapy for a short time but in the remaining 218 cases, the IOP raise was transient. In a similar study, Gismondi et al. investigated the IOP changes related with the IV injection of ranibizumab in ARMD cases. They measured IOP by Tonopen before and after injection (5 s, 5, 10, 15, 30, 60 min, and 1 day after the injection). They observed statistically significant raises in IOP within the 30 min but at the first hour and day, no significant differences were observed in IOP from the baseline [14]. In our study, we also observed a significant raise in IOP at the post-injection 30th minute.

In our study, we aimed to investigate the IOP changes due to the initial IV anti-VEGF injections

within the post-injection first month in non-glaucomatous cases. Like the previous reports, we examined significant increase in the mean IOP, 30 min after the injection. But interestingly, at the first day, first week and first month after the injection, we observed significant decreases in IOP than baseline values. One probable mechanism is ciliary body inflammation due to the IV injection like other ocular surgeries within the first postoperative month. Vitreous loss after the injection does not seem to be so sensible so cause of IOP decrease by vitreous loss is thought to be outside chance.

We also investigated the CCT differences after the IV injection. Güler et al. investigated the short-term effects of intravitreal bevacizumab on cornea and anterior chamber in their study [20]. They investigated CCT, simulated keratometry, anterior chamber depth and iridocorneal angle by Sirius topographer after bevacizumab injection but could not observe significant changes within the first post-injection month. Pérez-Rico et al. investigated corneal endothelium changes due to the IV injection of ranibizumab but observed no significant changes within the 6 post-injection month [16]. We also observed no significant changes in CCT within the first month.

In conclusion, the current study confirms the results of previous studies which showed the safety of initial IV injection of anti-VEGF agents for IOP elevation and CCT changes 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 should be carried out.

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