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Comparison of the effects of 3 different anti-VEGF drugs on cornea thickness, lens thickness and anterior chamber depth: Case-Control Study

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Abstract

To compare the long-term effects of 3 different anti-VEGF molecules on the lens, cornea and anterior chamber in phakic patients who have received consecutive intravitreal injections. 157 patients who did not have corneal pathology but were treated with 1.25mg/0.05ml intravitreal bevacizumab, 0.5mg/0.5ml ranibizumab or 2mg/0.05ml aflibercept injections due to diabetic macular edema were retrospectively analyzed in our clinic. Patients who received three consecutive monthly injections were included to the study. Corneal thickness, lens thickness and anterior chamber depth measurements which were taken before the injections, 1 month after the first injection, 1 month after the second injection, and 1 month after the third injection were used in the study. There was no statistical difference between the bevacizumab, ranibizumab, aflibercept and control group in terms of preoperative specifications such as number of patients, gender and age average. A statistically significant difference was found between the 4 anterior chamber depth measurements in the control group, Ranibizumab drug group, and Bevacizumab and Aflibercept drug groups ($p<0.001$, $p=0.026$; $p=0.07$, $p<0.001$, respectively). Anterior chamber depth of the Ranibizumab and Bevacizumab patients decreased in the first month and increased in the second and third months. However, anterior chamber depth of the Aflibercept patients increased over time. As a result of our study; we concluded that three different anti- VEGF drug molecules have an effect on the anterior camera.

Keywords: Bevacizumab, aflibercept, ranibizumab, anterior chamber

Introduction

Bevacizumab, Ranibizumab and Aflibercept are being used in the treatment of diseases such as diabetic macular edema, retinal vein occlusion and senile macular degeneration. Bevacizumab, which is a monoclonal antibody, can bind to all forms of VEGF-A. It is a molecule which is used to inhibit various neovascularization and shown to be beneficial in the previous studies. Ranibizumab is a high-affinity antibody particle which is formed by the recombinant DNA technology and can inhibit all biologically active isoforms and active proteolytic components of VEGF 10. Aflibercept, which can bond to VEGF-B and placental growth factor 1-2 with high affinity can also bond with all isoforms of VEGF-A. Fc field serves as a receptor trap for all VEGF-A isoforms [1-5].

Although retinal neovascularization is the most common indicative use of anti-VEGF agents, previous studies show that they also have an effect on iris, lens and corneal neovascularization or that agents have toxic effect [2.6-9]. This makes us consider that these structures also carry receptors on them.

In our study, we aimed to compare the long-term effect of 3

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different anti-VEGF molecules on lens, cornea and anterior chamber of phakic patients who received three consecutive dose injections on monthly basis.

Material and Methods

Our study covers the retrospective analysis of total of 157 patients who have been diagnosed with diabetic macular edema (DME) in our eye clinic during the period of January 2021 to December 2021. 35 patients were given ranibizumab as intravitreal injection (IVR), 42 patients were given bevacizumab as intravitreal injection (IVB), 44 patients were given aflibercept as intravitreal injection (IVA) and 36 patients remained in the control group. Patients with refractive surgery history, corneal dystrophies, contact lens history as well as patients who have undergone cornea, lens or anterior chamber surgery during the study period and patients whose treatment cannot be completed after first or second injections were not included to the study. Local ethics committee approval (Düzce University Ethics Committee for Clinical Studies 2022-70) was granted for the study. Furthermore, informed consent forms were signed and submitted by each patient according to the Helsinki declaration.

4 separate groups were created, namely patients taking intravitreal bevacizumab (Altuzan, Roche), intravitreal ranibizumab (Lucentis, Novartis), aflibercept (Eylea; Bayer) throughout their DME treatment and the control group. The non-injected eyes of the patients taking intravitreal injection under DME treatment were used for the control group.

A detailed medical record was taken from all patients. Ophthalmologic examination of the patients was done by means of best visual acuity (Snellen chart), intraocular pressure measurement with Goldman applanation tonometry, anterior and posterior segment analysis with biomicroscope , noncontact indirect fundus examination of dilated pupil with of 90 D lens, central macular thickness measurement (OCT) and only patients diagnosed with DME through FFA and treated with intravitreal injection are included to the study. Phakic cases who received three consecutive dose injections on monthly basis have been included to the study. There was one-month interval between the injections and patients were selected among the ones with no previous treatment. Central cornea thickness (CCT), anterior chamber depth (ACD), lens thickness (LT) measurements that were made before the injection, one month after the first injection, one month after the second injection and one month after the third injection were used. Ultrasonic pachymetry device, Echoscan US 500 system (Nidek Co. Ltd., Aichi, Japan), which is considered to be the golden standard method, was used for the measurements.

Intravitreal injections were done in sterile surgery rooms. Before the process, topical anesthetic eye drop Alcaine (Proparacaine, Alcon) was applied to the eye subject to injection. The patient than was placed on the surgery table where the periorbital region was washed with 10% povidone iodine (Isosol, Merkez) and a drape was placed followed by similarly washing the surface of the eye to be injected after opening the eye lid with the help of blepharostat. 0.05 ml agent of bevacizumab, ranibizumab or aflibercept is applied as intravitreal injection. 27 Gauge injection wass used during the process where the injection was done from the inferior temporal segment side, at a measured distance of 3.5 - 4 mm from limbus. Patients with no signs of complications were called in for controls after one month. CCT, ACD and LT measurements were done during the control period. Above mentioned procedures were applied to the second and third injections as well, followed by the same control steps 1 month after each injection.

All measurements were carried out by the same experienced ophthalmologist. Since all measurements were done by the same person, the data were admitted as the mean of measurements taken after the 3 injections in order to avoid any bias.

In all 3 groups, CCT, ACD and LT values of the patients, pre-injection and post-injection values as well as values after all three injections were compared both within themselves and with the control group.

The data received throughout the study were analyzed by the SPSS 25.0 version software. Distribution of the data were shown by descriptive analysis parameters (mean, standard deviation, minimum, maximum, frequency and percentage). The coherence of the data with the normal distribution was analyzed by Kolmogorov-Smirnov test. Analysis of variance, ANOVA was employed for the purpose of determining the effect of drug applications on CCT, ACD and LT. Mann Whitney U Test was used for the mean comparison of two independent groups whereas Kruskal Wallis H Test was used for the mean comparison of more than two independent groups. Spearman's Correlation Test was employed for the relation between two constant variables. Furthermore, in cases where Mauchly's sphericity assumption was violated and epsilon value was higher than 0.75 ($\varepsilon>0.750$), then Huynh-Feldt correction was used but if the epsilon value was less than 0.75 ($\varepsilon<0.75$), then Greenhouse-Geisser correction was used to correct the violation.

Results

The demographic specifications of the patients are shown in the table (Table 1). A total of 157 patients participated to the study where 22.9% is the control group, 22.2% is the Ranibizumab group, 26.8% is the Bevacizumab group and 28.1% is the Aflibercept group. A statistically significant difference was found between the groups in terms of age ($p=0.003$). There was no statistically significant difference between the groups in terms of gender distribution. ($p=0.556$).

Throughout the study, the changes in the cornea thickness over time due to drug application are compared and the results are analyzed in table (Table 2). Based on these results there is no statistically significant difference between the means of the cornea thickness measurements of the control group or injection

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applied groups that are done before the application as well as in the first, second and third months of the injection (p>0.05). Based on the results of simple main effect analysis over time, there is no statistically significant difference between the 4 cornea thickness measurements of the control group, Ranibizumab drug group, Bevacizumab drug group and Aflibercept drug group (p>0.05).

The changes in the lens thickness over time due to drug applications are compared in the study and the results are analyzed in the table (Table 3). Based on these results there is no statistically significant difference between the lens thickness of the control group or injection applied groups before the application nor in the first, second and third months after the application (p>0.05). Lens thickness of patients with no drug application and Aflibercept application tend to decrease over time. However, statistically significant difference was determined among the 4 lens thickness measurements of the Ranibizumab ad Bevacizumab drug groups (p<0.001, p=0.026, p=0.07, p<0.001 respectively). Anterior chamber depth of Ranibizumab and Bevacizumab groups have decreased in the first month but increased in the second and third months. However, anterior chamber depth of Aflibercept applied group has increased over time.

Table 1. Demographic Information Distribution of the Participating Patients

	Gender	n	%	X^2	p	Age		F	p
						X ± SS	Min - Max		
Control	Male	16	10.2	2.030	0.566	70.6±8.7	57-85	4.819	0.003
	Female	20	12.7						
Ranibizumad	Male	12	7.6			64.6±7.1	55-82		
	Female	23	14.6						
Bevacizumab	Male	21	13.4			65.5±6.9	50-79		
	Female	21	13.4						
Aflibercept	Male	18	11.5			64.3+9.2	52-86		
	Female	26	16.6						
Total		157	100						

SD: Standard Deviation

Table 2. Comparison of Drug Application and Change in the Cornea Thickness Over Time

Time		Control Group	Ranibizumab	Bevacizumab	Aflibercept	F	P
		X ± SS	X ± SS	X ± SS	X ± SS		
Cornea Thickness (µm)	0.Month	555.33±32.1	547.11±48.4	551.71±55.9	544.36±38.4	1.183	0.318
	1.Month	554.86±35.8	546.11±46.7	564.17±45.0	547.73±37.7	1.172	0.323
	2.Month	555.42±31.0	546.66±46.9	563.60±46.4	547.68±37.2	1.502	0.216
	3.Month	555.75±30.9	553.51±46.5	564.88±44.6	547.48±36.8	1.033	0.380
F		1.002	1.008	1.010	1.767		
p		0.324	0.323	0.321	0.190		

SD: Standard Deviation, µm: micrometer, statistically significant p value is taken as p<0.05 p value at the end of the table shows the inter-group changes and the p value underneath the table show the within-group changes

Table 3. Comparison of Drug Application and Change in the Lens Thickness Over Time

Time		Control Group	Ranibizumab	Bevacizumab	Aflibercept	F	P
		X ± SS	X ± SS	X ± SS	X ± SS		
Lens Thickness (mm)	0.Month	4.24±0.8	4.37±0.7	4.50±0.7	4.29±0.7	0.959	0.414
	1.Month	4.23±0.8	4.36±0.7	4.56±0.7	4.23±0.7	1.840	0.142
	2.Month	4.21±0.8	4.34±0.7	4.48±0.7	4.21±0.7	1.310	0.273
	3.Month	4.11±0.8	4.29±0.7	4.44±0.7	4.13±0.7	1.716	0.166
F		4.035	2.720	1.762	4.825		
P		0.044	0.098	0.190	0.014		

SD: Standard Deviation, mm: milimeter, statistically significant p value is taken as p<0.05 p value at the end of the table shows the inter-group changes and the p value underneath the table show the within-group changes

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Table 4. Comparison of Drug Application and Change in the Anterior Chamber Depth Over Time

Time		Control Group	Ranibizumab	Bevacizumab	Aflibercept	F	P
		X ± SS	X ± SS	X ± SS	X ± SS		
Anterior Chamber Depth (mm)	0.Month	2.92±0.6	3.02±0.5	3.04±0.4	2.91±0.6	0.705	0.551
	1.Month	3.15±0.4	3.01±0.6	2.94±0.6	3.03±0.5	0.979	0.405
	2.Month	3.19±0.5	3.09±0.5	3.05±0.5	3.15±0.5	0.621	0.603
	3.Month	3.15±0.4	3.21±0.5	3.17±0.5	3.17±0.5	0.091	0.965
F		13.646	3.985	5.296	16.398		
P		0.000	0.026	0.007	0.000		

SD: Standard Deviation, mm: milimeter, statistically significant p value is taken as $p<0.05$ p value at the end of the table shows the inter-group changes and the p value underneath the table show the within-group changes

Discussion

Intravitreal injections have been an important part of DME treatment in the recent 50 years. Hypoxia, hyperglycemia and inflammation play main role in DME formation but since VEGF is the main mediator that causes all these, the above mentioned 3 anti-VEGF agents used in the topical treatment during the disease pathogenesis provide both functional and anatomic improvement of the patients. Frequency of the intravitreal injection use rapidly elevates due to success in treatments and continuing resilience on individual based DME's however, increased amount of applied intravitreal injections bring along complications as well. These complications may end up with results such as conjunctival hemorrhage, increase in IOP, endophthalmitis and even complications that may lead to blindness [10-11].

Related studies have accelerated after reports of toxic reactions associated to cornea which seemed like a distant target for intravitreal injections [9]. In their study with 43 patients subject to 2.5 mg/0.1 ml intravitreal Bevacizumab, Güler et al. evaluated the post-injection results of the 3rd day, 15th day and 1 month. They found out that there was no statistically significant difference among these measurements in terms of CCT [12]. Herrorors et al., in their study with 26 patients with senile macular degeneration, evaluated the effects of applied IVR on cornea after 6 months. Ultimately, they did not find any statistically significant difference in terms of CCT [13]. Perez-Rico et al. found out that there was no statistically significant difference in terms of CCT after 6 months evaluation of 52 patients with IVR application [14]. In their study with 44 patients of IVA application, Muto et al. evaluated the first, third and sixth months and determined that there was no statistically significant difference in the 6-month results of CCT [15]. Arslan et al. found out no statistically significant difference in CCT evaluation of the 2 intravitreal injections in their study [16]. There was no previous study covering all 3 different anti-VEGF agents in the literature. Similar to previous literature, we did not find any statistically significant difference in the cornea thickness in our study either.

We did not find any previous literature related to the lens which is the closest neighbor after intravitreal injections are applied to vitreous. In their study of 37 patients with intravitreal dexamethasone implantation, Anayol et al. found out that the lens thickness increased in 3 months but there was no statistically significant difference [17]. Likewise, there was no statistically significant difference among the 4 groups in our study.

Although a decrease in ACD due to elevated vitreous pressure after intravitreal injection is expected, there is no sufficient data on the long-term effects. In their study of 46 patients with IVB application, Alkin et al. evaluated the effects in 5 minutes, 1 hour and 3 hours. They found statistically significant increase in ACD in terms of short-term effect [18]. In their study covering 3 different anti-VEGF comparison, Arslan et al. found a decrease in the anterior chamber depth after 2 intravitreal injection and suggested that the difference is statistically significant [16]. In our study, anterior chamber depth of the patients subject to Ranibizumab and Bevacizumab application decreased in the first month and increased in the second and third month. However, anterior chamber depth of the patients subject to Aflibercept application increased over time. As a result of literature review, no study was found that covered the comparison of different anti-VEGF molecules. We believe that the observed difference might be related to relatively low group counts.

We had a few limiting factors in our study. First one was to run the study in a single center. Second was not measuring the axial length and intraocular pressure values. Third was not using non-contact method in pachymetry measurements. The strength of our study, on the other hand, was being among the first studies in literature to evaluate 3 different anti-VEGF molecules in terms of anterior segment parameters.

Conclusion

The number of intravitreal injections keep increasing and complications related to this situation are also expected to increase. In our study, we compared the most commonly used 3 different anti-VEGF molecules. As a result of our study; we concluded that 3 different anti-VEGF molecules did not have an effect on CCT and LT but have a decreasing effect on ACD. We believe that repeating this study with a higher number of patients and on multi-centered basis would generate more reliable results

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thus enabling us to have a better understanding of the medication.

Conflict of interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that they have received no financial support for the study.

Ethical approval

Düzce University Ethics Committee for Clinical Studies 2022-70.

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