Original Article

Effect of Intravitreal Bevacizumab Injection on Corneal *in vivo* Biomechanics: A Pilot Study

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Abstract

Purpose: To evaluate the effect of intravitreal bevacizumab (IVB) injection on corneal biomechanical parameters as measured by the ocular response analyzer (ORA) and Corneal Visualization Scheimpflug Technology (CorVis).
Methods: In this prospective pilot study, ORA and CorVis parameters were recorded before and after a three-month course of IVB injection therapy in 16 patients in the injected and the contralateral non-injected control eyes. The changes in the recorded parameters in each group and the differences between the two groups were evaluated and compared.
Results: None of the changes in ORA parameters were statistically significant in the injected and non-injected groups before and three months after injection, except for corneal resistance factor (CRF) in injected eyes (paired *t*-test, $P = 0.039$). The differences in corneal hysteresis (CH) and CRF were not statistically significant between the two groups ($P = 0.441$ and 0.236, respectively), but significant differences were noted between corneal compensated IOP (IOPcc) and Goldmann-correlated IOP (IOPg) ($P = 0.045$ and 0.047, respectively). None of the changes in CorVis parameters were statistically significant in the groups before and at the end of study, except for the time of first corneal applanation (TAp1 ms) in the injected group ($P = 0.040$, paired *t*-test). Differences in TAp1, length of the second corneal applanation (LAp2 mm), velocity of the second corneal applanation (VAp2 m/s), intraocular pressure (IOP), and central corneal thickness (CCT) also showed borderline significance between the two groups.
Conclusion: In this pilot study IVB injection could change CRF, IOPcc, IOPg, and TAP1 as measured by ORA and CorVis.

Keywords: Bevacizumab; CorVis; Corneal Biometrics; Ocular Response Analyzer

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INTRODUCTION

Today, intravitreal injection of anti-vascular endothelial growth (anti- VEGF) factors has an important and

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ever-growing role in the treatment of retinovascular disorders. There is an ongoing application of anti-VEGF drugs to treat proliferative diabetic retinopathy, age-related macular degeneration, and retinal vein occlusion. On the other hand, there is little information on systemic or local effects on other ocular tissues. It has been shown that the connective tissue growth factor (CTGF)/vascular endothelial growth factor (VEGF) ratio is a strong predictor of vitreoretinal fibrosis in PDR, and that intravitreal anti-VEGF treatment causes increased fibrosis in eyes with PDR by increasing the level of CTGF.[1] The shift in balance between the levels of CTGF and VEGF in the eye is associated with this angiofibrotic switch; CTGF is correlated positively, while VEGF is correlated negatively with the degree of fibrosis. It has been reported that CTGF is found in many tissues including cornea and sclera.[2] Increased proportional level of CTGF has been reported to result in stimulated matrix contraction by fibroblasts in cornea during wound healing.[3] The same effect in unwounded cornea may result in a change in corneal stiffness or biomechanics. This shift can have unpredictable effects on other ocular tissues such as the sclera and cornea. To date, only two devices providing corneal biomechanical information and designed for clinical use are available: the Ocular Response Analyzer (ORA), a dynamic bidirectional applanation device, and the CorVis ST, a dynamic Scheimpflug analyzer device.[4] This pilot study was designed to investigate the possible effect of bevacizumab on *in vivo* corneal biomechanics through its possible effect on CTGF level and CTGF/VEGF ratio in the eye. To the best of our knowledge, this is the first such study in this field.

METHODS

This pilot study was performed at the Retina Research Center, Khatam Eye Hospital, Mashhad, Iran, from November 2014 to September 2015. Eligible participants were all adults who met the inclusion criteria for intravitreal injection of bevacizumab for recently recognized choroidal neovascularization (CNV) or retinovascular accident. The exclusion criteria were: a positive history of intraocular surgery, keratorefractive surgery, ocular trauma, keratoconus, corneal dystrophy, retinal scar, or diabetes mellitus. Both eyes of each patient were included in the study; however, only the eye with retinal pathology received intravitreal bevacizumab and the other eye served as the control eye.

This pilot study was approved by the Review Board/Ethics Committee of the Retina Research Center, Mashhad University of Medical Sciences. The study protocol was explained to all patients and written informed consent was obtained from each patient.

All eligible eyes received three doses of intravitreal bevacizumab (1.25 mg, 0.05 mL) at four-week intervals. Bevacizumab (Avastin made for F. Hoffmann- La Roche Ltd. Basel, Switzerland by Genentech Inc., San Francisco, CA, USA) was injected intravitreally with a 30-gauge needle into the superotemporal quadrant, 3.5-4 mm from the limbus in pseudophakic and phakic eyes, respectively. Complete ophthalmic examination including best corrected visual acuity, intraocular pressure (IOP), and retinal exam were performed at each visit. Corneal biomechanical parameters were tested using ocular response analyzer (ORA; Reichert Inc, Depew, NY) and CorVis (Oculus, Wetzlar, Germany) in both eyes before intravitreal injection and one month after the last injection.

The authors did not check any test-retest accuracy for their ORA and CorVis measurements and for eliminating this variability, a minimum of four ORA and CorVis readings of good quality with symmetric peak heights, similar width, and a waveform score (WS) of more than 5 were considered for the study inclusion. An experienced investigator judged the response profile quality based on the criteria provided by the manufacturer. The best signal value, as selected by the computer software (ORA version 3.01), was used to eliminate selection bias. An experienced technician, who was blinded to the identity of the eye that had received the treatment, obtained the measurements to avoid inter-observer variability in the results.

The parameters of corneal hysteresis (CH) and corneal resistance factor (CRF) were measured using ORA as well as for the noncontact assessment of IOP, described as Goldmann-correlated IOP (IOPg) and corneal compensated IOP (IOPcc).

The parameters measured by CorVis were as follows: IOP, time of the first corneal applanation (TAp1 ms), length of the first corneal applanation (LAp1 mm), velocity of the first corneal applanation (VAp1 m/s), time of the second corneal applanation (TAp2 ms), length of the second corneal applanation (LAp2 mm), velocity of the second corneal applanation (VAp2 m/s), pachymetry of the apex (pachy μm), highest amplitude of corneal deformation or amplitude deformity (HAD mm), central curvature radius at the moment of highest concavity (RHC mm), peak distance between the two corneal peaks in the highest concavity (PDHC mm), and the time from the beginning to the highest concavity of the cornea (THC ms).

The primary outcome measures included comparing the changes in the ORA and CorVis parameters before and after IVB injection in the treated and control eyes. Secondary outcome measures included comparing differences in ORA and CorVis parameters before and after IVB injection in the treated and control eyes. Patient data were recorded in data collection sheets. Statistical analysis was performed with SPSS13 (Statistical Package for Social Sciences version 13.0, SPSS Inc. Chicago, IL). Qualitative variables were expressed using percentages, and quantitative data were explained with mean,

standard deviation, and/or confidence interval. T-test and Chi-square test were used for inferential statistics. Normal distribution of quantitative data was checked using Kolmogorov-Smirnov test. The level of significance was 0.05 ($\alpha = 0.05$).

RESULTS

After screening, 21 patients met the inclusion criteria and were enrolled in this pilot study. In two patients with diagnosis of branch retinal vein occlusion (BRVO), macular edema resolved with one IVB injection and no further injection was administered. Three patients did not complete the three-month follow up. Finally, 16 patients completed the follow-up and were eligible for statistical analysis.

The mean (±SD) age of patients was 50.1 ± 14.9 years (range: 25-79 years). Six patients (37.5%) were male. The indication for IVB was CNV in five eyes, BRVO in eight eyes, and central retinal vein occlusion (CRVO) in three eyes. Mean baseline and final visual acuities were 1.07 ± 0.47 logMAR and 0.66 ± 0.73 logMAR in the treated eye and 0.18 ± 0.32 logMAR and 0.28 ± 0.41 logMAR in the control eye, respectively. Changes in BCVA were statistically significant in the treated group ($P = 0.026$ in treated eyes and $P = 0.41$ in control eyes, paired *t*-test). The demographic data of patients are summarized in Table 1.

ORA Findings

All ORA findings are summarized in Table 2. Corneal hysteresis (CH), CRF, IOPg, and IOPcc were evaluated using ORA. In the injected eyes, CRF increased significantly from 9.31 ± 1.49 mmHg before injection to 9.48 ± 1.75 mmHg after injection (paired *t*-test, $P = 0.039$). The changes in the other ORA parameters from the start to the end of the study were not statistically significant. In control eyes, the changes from the start to the end of the study in all ORA parameters were not statistically significant. Differences in ORA parameters were also calculated between injected and control groups. Differences in CH and CRF were not statistically significant ($P = 0.441$ and 0.236, respectively), but those between IOPcc and IOPg were statistically significant between the two groups ($P = 0.045$ and 0.047, respectively).

CorVis Findings

All CorVis findings are summarized in Table 3. Within the injected and control groups, the changes in all the CorVis parameters from the start to the end of the study were not statistically significant, except for TAP1 in the injected group ($P = 0.040$, paired *t*-test). Considering the differences of parameters in the injected and control groups, statistical analysis showed that IOP measurement in the injected group showed a significant increase. The mean difference in IOP (IOP at baseline minus IOP at the end of study) was −2.4 ± 4.0 mmHg in the injected eyes and −0.33 ± 1.66 mmHg in the control eyes ($P = 0.048$). Values for TAp1, VAp2, and LAp2 also showed borderline significant variations between the two groups. In TAp1, the injected eyes showed a difference of −0.49 ± 0.60 ms while control eyes had a difference of −0.21 ± 0.35 ms ($P = 0.084$). The difference in VAp2 was 0.01 ± 0.29 m/s in the injection group and −0.13 ± 0.17 m/s in control eyes ($P = 0.087$). The same data were 0.47 ± 0.64 mm and 0.10 ± 0.51 mm, respectively, for LAp2 ($P = 0.068$). An interesting finding was the difference in the change in thickness between the injected and control eyes; 13.78 ± 29.22 µm in the injection group and −2.11 ± 7.61 µm in controls ($P = 0.032$). The

Table 1. Demographic data of patients

Diagnosis (Involved eye)	Number	Age (Mean±SD) (Range)	Pre BCVA (Mean±SD)	Post BCVA (Mean±SD)
CNV	5	54.8±15.6 (38-79)	0.12±0.22	0.44±o. 43
BRVO	8	54.3±9.0 (42-66)	0.28±0.40	0.31±0.46
CRVO	3	35.3±16.2 (25-54)	0.00±0.00	0.00±0.00
Total	16	50.1±14.9 (25-79)	1.07±0.47	0.66±0.73

SD, standard deviation; CNV, chroidal neovascularization, BRVO, branch retinal vein obstruction; CRVO, central retinal vein obstruction; BCVA, best corrected visual aquity; LogMAR, logarithm minimum angle of resolution

Table 2. ORA findings before and after injections

	Injected group			Control group			Difference		
	Before Mean±SD	After Mean±SD	*P*	Before Mean±SD	After Mean±SD	*P*	Injected Mean±SD	Control Mean±SD	*P*
CH	9.45±1.53	9.48±1.53	0.733	9.71±1.36	10.15±1.46	0.641	0.12±1.00	-0.21±1.30	0.441
CRF	9.31±1.49	9.48±1.75	0.039	9.65±1.15	10.18±1.79	0.279	-0.83±0.98	-0.42±1.06	0.236
IOPcc	16.21±5.40	18.86±5.98	0.102	16.50±4.80	16.18±5.02	0.894±	-2.78±4.37	-0.13±2.81	0.045
IOPg	14.56±5.14	17.67±6.01	0.067	14.93±4.31	1542±5.17	0.641	-3.05±4.20	-0.75±2.23	0.047

CH, corneal hysteresis; CRF, corneal resistance factor; IOPg, goldmann-correlated IOP; IOPcc, corneal compensated IOP; *P, P value*

Table 3. CorVis findings before and after injections

	Injected group			Control group			Difference		
	Before Mean±SD	After Mean±SD	*P*	Before Mean±SD	After Mean±SD	*P*	Injected Mean±SD	Control Mean±SD	*P*
TAP1	7.10±0.50	7.69±0.66	0.04	7.08±0.54	7.29±0.50	0.121	-0.49±0.60	-0.21±0.35	0.084
LAP1	1.75±0.47	1.74±0.24	0.735	1.66±0.25	1.78±0.26	0.492	-0.03±0.23	-0.11±0.43	0.256
VAP1	0.13±0.03	0.12±0.02	0.745	0.12±0.02	0.12±0.04	0.800	-0.00±0.04	-0.00±0.04	0.537
TAP2	21.16±0.58	21.54±2.36	0.537	21.15±0.49	21.00±0.63	0.524	-0.82±3.17	0.85±0.37	0.239
LAP2	1.96±0.48	1.66±0.52	0.096	2.00±0.33	1.93±0.42	0.591	0.47±0.64	0.10±0.51	0.068
VAP2	-0.37±0.10	-0.34±0.21	0.911	-0.39±0.10	-0.29±0.12	0.069	0.01±0.29	-0.13±0.17	0.087
IOP	14.92±2.88	18.23±4.39	0.116	15.11±2.66	15.73±3.13	0.576	-2.44±4.04	-0.33±1.66	0.048
Pachy	514.69±42.52	503.64±33.89	0.207	502.15±26.56	505.00±32.17	0.433	13.79±29.22	-2.11±7.61	0.032
HAD	1.03±0.13	0.90±0.19	0.135	1.01±0.12	0.96±0.14	0.116	0.07±0.11	0.05±0.04	0.502
RHC	7.27±0.82	8.07±2.03	0.373	7.30±0.95	7.77±1.16	0.278	-0.72±1.90	-0.31±0.79	0.418
PDHC	4.79±0.35	4.31±1.09	0.248	4.86±0.29	4.77±0.37	0.309	0.45±0.98	0.05±0.13	0.094
THC	16.30±0.80	15.55±0.82	0.117	15.94±0.51	15.65±0.52	0.174	0.76±1.20	0.26±0.51	0.107

IOP mmHg, intraocular pressure; TAp1 ms, time of the first corneal applanation; LAp1 mm, length of the first corneal applanation; VAp1 m/s, velocity of the first corneal applanation; TAp2 ms, time of the second corneal applanation; Lap2 mm, length of the second corneal applanation; VAp2 m/s, velocity of the second corneal applanation; pachy µm, pachymetry of the apex; HAD mm, highest amplitude of corneal deformation or amplitude deformity; RHC mm, central curvature radius at the moment of highest concavity; PDHC mm, Peak distance between the two corneal peaks in the highest concavity and THC ms the time from the beginning to the highest concavity of the cornea

other variables showed no statistically significant difference between the two groups.

DISCUSSION

There are some known side effects of IVB injection such as endophthalmitis or retinal break, but there is a lack of studies regarding the localized or systemic effects of this procedure. Anti-VEGF drugs may influence the balance of some mediators in the eye. Adjacent and nontarget tissues such as the cornea may be inadvertently affected during the procedure. The aim of this pilot study was to investigate whether intravitreal bevacizumab injection affects the biomechanical parameters of the cornea.

The post-bevacizumab fibrotic phenomenon has been observed previously in PDR as well as in age-related macular degeneration by Wu and Martinez et al.[5] Connective tissue growth factor (CTGF) has been found to play an important role in promoting fibrosis and scarring in numerous tissues, including the cornea, and promoting the synthesis of various constituents of the extracellular matrix and plays a critical role in fibroproliferative effects of corneal fibroblasts.[6-8]

He and Chen et al identified CTGF as a major mediator of retinal fibrosis and a potentially effective therapeutic target.[9] Kuiper and Van Nieuwenhoven et al hypothesized that a shift in the balance between CTGF and VEGF is associated with the switch from angiogenesis to fibrosis in proliferative retinopathy.[10] These findings provide strong support for the model that a reduction in VEGF levels after intravitreal injection of anti-VEGF agents leads to accelerated fibrosis by causing a shift in the CTGF/VEGF balance in favor of CTGF. Progression or development of traction retinal detachment or a fibrotic switch has been observed in diabetic fibrovascular proliferative membranes after bevacizumab administration.[11,12] Bevacizumab also exerts a pro-fibrotic effect on human retinal pigment epithelial cells at clinical doses and may be one of the underlying mechanisms for IVB-associated complications.[13] Although we should consider that many other factors can play a role in corneal biomechanical changes, and the role of CTGF has not been definitively determined in this field, the cited studies suggest that an imbalance between CTGF and VEGF in favor of CTGF, induced by multiple injections of IVB, may affect the elasticity, stiffness, or other biomechanical parameters of the cornea by activating fibroblast cell receptors.

The exclusion criteria in our study were somewhat strict because many factors may influence the biomechanical parameters of cornea by themselves. Diabetes has a natural effect on corneal stiffness and elasticity. Diabetes mellitus causes stromal changes including structural alterations produced by collagen crosslinking and increased stiffness of the cornea, affecting the biomechanical parameters of the human cornea.[14-16] Some studies have reported a reduction in CH and CRF in diabetic patients while others have reported the opposite.[17]

The interpretation of biomechanical parameters of the cornea is difficult. Additionally, arriving at a true and accurate evaluation of corneal characteristics is not an easy task because of the complexity of the corneal viscoelastic biomechanical response. There are only two devices designed to provide corneal biomechanical data for clinical use: the Ocular Response Analyzer and the CorVis ST, a dynamic Scheimpflug analyzer device. We found some changes in corneal biomechanical parameters after three injections of IVB, as measured by CorVis

and ORA. In injected eyes, CRF increased significantly from 9.31 ± 1.49 mmHg to 9.48 ± 1.75 mmHg after injection (paired *t*-test, $P = 0.039$). Changes in values for TAp1, VAp2, and LAp2 also showed borderline significant differences between the two groups in repeatability study of CorVis measurements. Hon and La et al found that the most repeatable corneal parameter measured by this device was CCT, followed by HAD, TAp1, and IOP which have good intersession reproducibility.[18] As we excluded diabetes and other factors that may affect corneal biomechanical behavior, we believe that these changes are directly attributable to the effects of IVB on the cornea by changing the balance of CTGF/VEGF in the eye.

IOP rise may be associated with intravitreal anti-VEGF injections as described in some reports.[19,20] It was proposed by Tseng and Vance et al that ranibizumab may block the outflow pathways of the eye by an unknown mechanism for several weeks or months.[21] Another explanation is an underlying inflammatory or immunological reaction that damages the aqueous humor outflow pathways.[22,23] A traumatic mechanism leading to a disruption of the anterior hyaloid or zonules and allowing access for high molecular weight proteins to enter the anterior chamber, resulting in increased IOP has been reported by Menke and Salam et al.[24]

We did not find a significant change in IOPg and IOPcc as measured by ORA, or in IOP as measured by CorVis in our pilot study before and after three IVB injections; however, the difference in IOP: IOPcc, IOPg, and IOP was statistically significant between the two groups with increased IOP reported after injection. The changes in IOPcc and IOPg were significantly higher in injected eyes (P value = 0.045 and 0.047, respectively) and the mean change in IOP measurement from baseline as measured by CorVis was −2.4 ± 4.0 in injected eyes and −0.33 ± 1.66 in control eyes ($P = 0.048$). According to our findings, another explanation for IOP change after intravitreal anti-VEGF injections is the change in corneal biomechanical behavior which should be considered in calculating the exact IOP in these patients. This means that a correcting factor may be necessary in calculating the true IOP in patients who have had multiple IVB injections, most probably dependent on the number of injections administered. The exact effect of IVB on IOP via corneal biomechanical behavior changes needs further investigation.

In ORA, the CH and CRF are related to the elastic properties of the cornea. In our pilot study, the CRF in the injected eyes increased significantly. This may be due to increasing elasticity and stiffness of cornea induced by increased CTGF in these eyes. It should be noted that this study is a pilot study with a small sample size and the statistical significance may simply be due to the number and range of measurements. It is quite clear that the small difference observed in CRF in the current study may have no clinical significance.

Mean values of CH are between 9.3 ± 1.4 mm Hg and 11.43±0.52 mm Hg and of CRF between 9.2 ± 1.4 mm Hg and 11.9 ± 1.5 mm Hg in the peer-reviewed literature. Therefore, there is a significant variability in CH and CRF among normal healthy individuals.[4] In our pilot study, the mean CH and CRF were comparable to previously described values in the literature.

Corneal biomechanical parameters decrease with age without significant changes in CCT or IOP. On the other hand, the cornea becomes considerably stiffer with age.[25,26] Some authors report a tendency toward lower values of CH and CRF in black subjects compared to white subjects.[27] Other factors can influence CH and CRF in the healthy eye; for example, CH and CRF temporarily decrease during ovulation.[28] We did not consider these probable confounding factors in our pilot study because of the small sample size.

The difference in thickness between injected and control eyes was statistically significant at 13.78 ± 29.22μm in the injection group and −2.11 ± 7.61μm in controls ($P = 0.032$). In the previous studies by Raluca and Monali et al, safety of bevacizumab on corneal endothelial cells has been reported.[29] This decrease in corneal thickness, as measured by CorVis, may be due to the changes in the constituents of the extracellular matrix of cornea caused by increased CTGF levels in these eyes. Again, it should be emphasized that this is a pilot study, and the precision of our results is uncertain.

In conclusion, according this pilot study, IVB can change certain biomechanical functions of the cornea as measured by ORA and CorVis. Our results and the clinical importance of these changes need further investigation in studies with a larger sample size.

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Nil.

Conflicts of Interest

There are no conflicts of interest.

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