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Peripapillary Perfusion Changes Influenced by Intravitreal Ranibizumab in Diabetic Macular Edema Patients– an OCT Angiography Study

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Abstract:

Background: Optical coherence tomography angiography (OCTA) is a method for noninvasively visualizing the vascular function of Optic Nerve Head (ONH) at the capillary level. A significant reduction in Optic Nerve Head vascular function has been found in a rat model of high intraocular pressure utilizing optical coherence tomography angiography. Aim: To assess the influence of intravitreal injection of anti VEGF Ranibizumab (Lucentis) on peripapillary capillary perfusion in diabetic macular edema patients by OCTA. **Patients and methods:** A prospective cohort cross-sectional interventional research. This study was conducted in ophthalmology department and outpatient follow-up retina unit, Benha university hospital. Time of the study: from August 2023 till January 2024. **Results:** Superior RPC density significantly increased from 48.3 ± 6.17% to 50.8 ± 6.19% (P=0.01), and whole disc RPC density (all vessels) rose from 47.6 ± 3.77% to 55.1 ± 4.12% (P<0.001). Inferior RPC density showed no significant change (P=0.06). IOP changes were insignificant (17.3 ± 1.84 mmHg to 19.3 ± 4.74 mmHg, P=0.06). **Conclusion:** Intravitreal Ranibizumab significantly enhances peripapillary and whole disc perfusion in DME patients without significant IOP elevation. Long-term effects on ONH perfusion require further investigation.

Key words: Diabetic macular edema; Ranibizumab; OCT angiography.

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Introduction

OCTA is a method utilized to noninvasively visualize the vascular function of Optic Nerve Head at the capillary level. A significant reduction in Optic Nerve Head vascular function has been found in a rat model of high intraocular pressure utilizing optical coherence tomography angiography [1-3].

Annually, millions of intravitreal antivascular endothelial growth factors (anti VEGF) injections are administered to manage various retinal vascular disorders, involving diabetic macular edema, retinal vein obstruction, in addition neovascular age-related macular degeneration. A standard volume of antivascular endothelial growth factor drug (0.05 milliliters) is injected into the vitreous cavity, resulting in a usual increase in intraocular pressure due to the eye's restricted compliance [4,5].

Though the elevation of intraocular pressure is often transient & resolves within thirty minutes, this temporary increase presents a distinctive opportunity for studying ONH response to an acutely elevated Intraocular Pressure. This investigation is to examine alterations in Optic Nerve Head perfusion prior to and immediately vs. 2 weeks following, an intravitreal injection utilizing Optical coherence tomography angiography to assess if the acute increase in Intraocular Pressure Influences Optic Nerve Head perfusion [6,7].

OCTA can extract blood flow signals by determining time differences in the OCT signal at the same site, with the intensity of the flow signal correlating with the number of red blood cells passing the vessel cross-section, that is, flux of blood flow [8]. Earlier investigations have shown that Optical coherence tomography angiography utilizing the OMAG algorithm can image retinal vessels and small capillaries in both Optic Nerve Head and the peripapillary region, exhibiting great reproducibility & repeatability in comparison with conventional approaches [9].

Our study aimed to assess the influence of intravitreal injection of anti VEGF Ranibizumab (Lucentis) on peripapillary capillary perfusion in diabetic macular edema patients by OCTA.

Patients and methods

A prospective cohort cross-sectional interventional research. This research was conducted in ophthalmology department and outpatient follow-up retina unit, Benha university hospital. Time of the study: from August 2023 till January 2024.

Inclusion criteria: All subjects enrolled in this research have been previously identified with diabetic retinopathy and diabetic macular edema(clinically significant macular edema - CSME), retinal thickening wihin 500 microns of fovea or any retinal thickening involving the fovea and existence of hard exudates within 500 microns of the fovea, only controlled type 2 diabetic cases have been involved to prevent bias in the investigation results, age > 18 years (Range 30-60 y) and all subjects enrolled in this study were receiving their first injection of Lucentis.

Exclusion criteria: Cases having a history of ophthalmic operations, other than uncomplicated cataract operations, have been excluded, as were those with active eye infections or ocular surface illness that would preclude the measurement of intraocular pressure or high-quality imaging utilizing Optical coherence tomography angiography and cases with retinal vascular changes other than diabetes. For instance, Myopic degeneration, uveitis and dystrophies, optic nerve diseases and glucoma patients and systemic vascular diseases. We excluded subjects whose images were of poor quality at baseline or at the initial post-injection time point Eyes exhibiting signal strength (SS) under the manufacturer's suggested cutoff (SS below six) or demonstrating significant eye

movement (subjectively characterized by image artifacts on the Optical coherence tomography face images, like a horizontal frame shift greater compared to the average diameter of retinal vessels or a distorted oval appearance of the Optic Nerve Head)—were excluded at baseline or during the initial post-injection point.

Sample size:

The study was conducted on twenty eyes of cases had type 2 controlled diabetes mellitus to receive their first intravitreal anti-VEGF Ranibizumab (Lucentis) injection who were admitted to our ophthalmology unit. The sample size was calculated using Epi info, version 3, opensource calculator with Cl .95% and power 80%. This yielded a total sample size of twenty patients [(9)].

Methods

All patients have been subjected to the following:

Complete history taking: Baseline characteristics involving patient ethnicity, gender, age, ocular and medical history, and ocular drugs have been gathered, **dilated pupil fundus examination** by indirect ophthalmoscope and slit lamp, **a baseline Intraocular Pressure of the eye** scheduled for an injection has been calculated utilizing an applanation tonometer, a minimum thirty minutes prior to injection. The average of three intraocular pressure measurements has been documented for each Intraocular Pressure measurement, and **blood pressure (BP) measurements** have been gained prior to imaging. The mean ocular perfusion pressure has been determined utilizing the formula (2/3) × (mean arterial pressure) − Intraocular Pressure, where mean arterial pressure is defined as diastolic Blood Pressure + (1/3) × (systolic Blood Pressure − diastolic Blood Pressure).

Procedures

The imaging procedure utilized is the CIRRUS HD-OCT 5000, utilizing the Angio Plex OCT Angiography system (center wavelength at 840 nanometer) with active motion tracking to reduce the influence of involuntary eye motion (Carl Zeiss Meditech Inc., Dublin, CA). The 4.5 millimeters × 4.5 millimeters en face OCTA image has been centered on the optic nerve head. The peripapillary area has been overlaid with annular contour lines of two millimeters and four millimeters in diameter around the disc margin. The peripapillary area was additionally categorized into eight sectors based on Garway-Heath's map. The built-in software automatically determines RPC VD utilizing Garway-Heath's map. The global RPC VD is assessed from the 360-degree annular peripapillary area. The RPC VD of the inferior and superior hemifield has been assessed from the superior and inferior sectors, correspondingly. Each Optical coherence tomography angiography scan cube covered a 2.4×2.4-millimeter square area. One B-scan had 245 A-scan sampling points. A total of 245 transverse sites has been acquired with four consecutive B-scans performed at each site. Baseline images have been gained within one hour prior to injection. Each A-scan had 1024 sampling points generated along two millimeters axial scan depth. Case s subsequently received the scheduled intravitreal antivascular endothelial growth factor Ranibizumab injection according to standard protocol. Prior to the application of anti-VEGF injection, the eyes have been managed with topical proparacaine hydrochloride (0.5 percent), topical tetravisc, and a topical five percent povidone-iodine solution. An eyelid speculum has been placed. The intravitreal injection has been given 3.5 or 4 millimeters from the limbus, in the inferotemporal quadrant, using a 30-G needle. Each patient received an injection of 0.05 milliliters of drug. Immediately to the injection, the eye has been irrigated with sterile eyewash. Optical coherence tomography angiography images centered at the Optic Nerve Head have been acquired after a single intravitreal

injection, utilizing the previously described protocol. The Intraocular Pressure has been determined prior to and two weeks following intravitreal injection. Topical anesthetic and fluorescein minims were used for IOP measurement using applanation tonometry with disposable cones. The period between injection & each image acquisition has been documented. Injected eyes have been imaged two weeks after the procedure to assess changes in papillary capillary perfusion.

Ethical Consideration

An official written adminstrative permission letter was aobtained from ethical committee of Benha University (Benha University Institutional Review Board IRB) {M.S.25.6.2023}, head of the department of ophthalmology in the same university. The investigation has been explained to them to ensure their cooperation. Any participant has the right to leave the study with no threat or persecution. Written informed consent has been gained from all participants. The research will be permitted by the ethics committee on investigation including human subjects of Benha faculty of medicine.

Statistical Analysis

Information analysis has been performed utilizing SPSS version 27 (IBM Corp, Armonk, NY, USA) For categorical data, descriptive statistics have been represented as percentages and numbers, whereas for normally distributed numeric variables, the mean and SD were applied. The paired sample t-test has been utilized to compare variables prior to and following intravitreal Ranibizumab injection, while the correlation coefficient was conducted by Pearson association. The P value below 0.05 is regarded significant.

Results

Table 1 shows that this interventional study included twenty eyes of 20 type 2 diabetes patients who received an intra-vitreal anti-VEGF Ranibizumab (lucentis) injection, their ages varied from 42 to 58 years with mean of 50.5 years ± 0.51 SD, half of them were males and the other half were females.

Table 2 shows that baseline IOP mean was 17.3 mmHg, while after intervention IOP meant 19.3, but this variance was not statistically significant (P above 0.05).

Table 3 shows that baseline superior RPC density % mean was 48.3 ± 6.17, while after intervention superior RPC density % mean significantly increased to 50.8 ± 60.19 (P=0.01). As regards baseline inferior RPC density % mean, it was 48.6 ± 4.03, while after intervention inferior PRC density%meanwas51.1 ± 5.54, with insignificant Differences (P above 0.05).

Table 4 shows that baseline whole disc small vessels RPC density % mean was 47.7 ± 3.77, while after intervention RPC density % mean significantly increased to 49.2 ± 3.86 (P=0.02). Similarly, baseline whole disc all vessels RPC density % mean was 47. 6 ± 3.77, while after intervention RPC density % significantly increased to 55.1 ± 4.12 (P<0.001).

Table 5 shows that baseline peripapillary small vessels RPC density % mean was 48.7 ± 5.8, while after intervention RPC density % mean significantly increased to 50.5 ± 6.2 (P=0.04). Similarly, Baseline peripapillary all vessels RPC density % mean was 56.1 ± 6.2, while after intervention RPC density % mean significantly increased to 57.7 ± 5.9 (P=0.04).

Table 6 shows that baseline peripapillary inferior small vessels RPC density % mean was 48.5 ±3.9, while after intervention RPC density % mean was 51 ± 5.6, with no significant change (P>0.05). Similarly, Baseline peripapillary inferior all vessels RPC density % mean was 55.4 ± 4.4, while after intervention RPC density % mean was 57 ± 4.9 with no significant change(P>0.05).

Table 1: Baseline characteristic among studied patients

	All patients (n =20)	
Age (years)	**Mean±SD**	**Range**
	50.5±0.51	(42 – 58)
Sex	**Male (N. %)**	**Female (N. %)**
	10 (50%)	10 (50%)

Table 2: Comparison of IOP prior to and following intervention.

	Before intervention	**After intervention**	**test**	**P-value***
IOP				
Mean±SD	17.3 ± 1.84	19.3±4.74	1.97	0.06

*: Paired sample t-test, P-value not more than 0.05: Significant, P above 0.05: Non-significant

Table 3: Comparison of superior & inferior RPC density %

RPC Density (%)	**Before intervention**	**After intervention**	**test**	**P-value***
Superior				
Mean±SD	48.3 ± 6.17	50.8 ± 60.19	2.87	**0.01**
Inferior				
Mean±SD	48.6 ± 4.03	51.1 ± 5.54	1.99	0.06

Table 4: Comparison of whole disc RPC density %

Whole disc	**Before intervention**	**After intervention**	**test**	**P-value***
Small vessels				
Mean±SD	47.7 ± 3.77	49.2 ± 3.86	-2.46	**0.02**
All vessels				
Mean±SD	47.6 ± 3.77	55.1 ± 4.12	-7.71	**<0.001**

Table 5: Comparison of Peripapillary superior RPC density % before and after intervention

Peripapillary superior	**Before intervention**	**After intervention**	**test**	**P-value***
Small vessels				
Mean±SD	48.7 ± 5.8	50.5 ± 6.2	2.2	**0.04**
All vessels				
Mean±SD	56.1 ± 6.2	57.7 ± 5.9	2.1	**0.04**

Table 6: Comparison of Peripapillary inferior RPC density % before and after intervention

Peripapillary inferior	**Before intervention**	**After intervention**	**test**	**P-value***
Small vessels				
Mean±SD	48.5 ±3.9	51 ± 5.6	2.1	0.051
All vessels				
Mean±SD	55.4 ± 4.4	57 ± 4.9	1.6	0.12

Discussion

Our results showed that this interventional study included twenty eyes of 20 type 2 diabetes patients who received an intra-vitreal anti-VEGF Ranibizumab (lucentis) injection, their ages varied from 42 to 58 years with mean of 50.5 years ± 0.51 SD, half of them were males and the other half were females.

In the current study we found that pre-injection mean IOP was 17.5 ± 1.84 mmHg (min = 15, max = 21), while the 2 weeks post-injection IOP was 19.5 ± 4.74 mmHg (min = 14, max = 30). A statistically insignificant variance between

the measured parameters pre- and post-injection.

In line with our results, Wen et al [9], stated that Following intravitreal anti-VEGF injection, a significant rise in intraocular pressure has been noted, as well as diminutions in flux, in vessel area density and normalized flux in the injected eyes at both post-injection timepoints, achieving significance at the 2nd timepoint. No significant variance in any of the three variables has been seen in the un-injected fellow eye. This recommends that the acute increase in intravitreal antivascular endothelial growth factor injection impairs ONH perfusion, and this impairment is unlikely to attributable to systemic factors injected by the un-injected fellow eye remains unaffected. Moreover, outcomes suggest that the autoregulation of blood flow to the optic nerve appears to give robust short-term compensation for acute intraocular pressure rise.

Intravitreal injections of anti-VEGF agents, such as ranibizumab can cause short-term increases in IOP. SAIF et al [10], stated that there was a statistically significant but clinically insignificant elevation in intraocular pressure (IOP) 24 hours following the intravitreal injection of ranibizumab, but the IOP remained within the normal range. The increase in IOP observed at 24 hours was transient, and there was no significant variance in Intraocular Pressure from 1 week to 8 weeks after the injection. The study confirms the safety of initial intravitreal injection of antiVEGF agents, such as ranibizumab, in terms of IOP elevation in non-glaucomatous patients for up to two months after the injection. While most studies indicate that anti-VEGF injections are safe for IOP in non-glaucomatous patients, regular monitoring is recommended due to the potential for sustained IOP elevation in some cases.

In the present study we found that mean pre-injection superior RPC vessel density was 48.25±6.17 (min = 35, max = 59), while the mean post injection superior RPC VS. Density was 50.80± 6.19 (min = 42, max = 46.5), and there was a statistically significant variance in the better RPC VS. density between pre- and post-injection, as the post-injection superior RPC VS. Density was higher with a mean difference of 2.55. While the inferior RPC vessel density showed no statistically significant variance among prior to and following injection, as the mean pre injection inferior RPC vessel density was 48.60± 4.03 (min = 43, max = 61) and the post injection inferior RPC vessel density was 51.11± 5.54 (min = 37, max = 62).

Our current findings clearly revealed that there was a statistically significant variance in the small BV whole image RPC vessel density pre- and post-injection. The pre-injection small BV whole image RPC VS. Density was 47.65± 3.77 (min = 40.6, max = 55.6), while the post injection small BV whole image RPC VS. Density was 49.69± 3.87 (min = 44.6, max = 58.2) with a mean variance of 2.02. There was no statistically significant variance in the All-BV whole image RPC vessel density between pre- and post-injection.

Abd-Elnaby et al. [11] showed that intravitreal ranibizumab treatment significantly enhanced best-corrected visual acuity (BCVA) in cases that had diabetic macular edema. Intravitreal ranibizumab treatment significantly reduced central foveal thickness (CFT) in cases that had diabetic macular edema. Intravitreal ranibizumab treatment significantly increased choriocapillaris vessel density in the subfoveal area of cases had diabetic macular edema.

Toto et al. [12] stated that there was a significant diminution in retinal capillary nonperfusion area (RCNPA) in the superficial capillary plexus (SCP) at one month following the first intravitreal ranibizumab injection, but this effect was lost at later time points. There was a trend towards a reduction in RCNPA in the deep capillary plexus (DCP) 3 months after the

first injection, but this was not statistically significant. There were insignificant changes in retinal capillary vessel density (RCVD) in either the SCP or DCP at any time point.

In the present study we found that small BV superior hemisphere RPC vessel density peripapillary showed a statistically significant variance among prior to and following injection. The mean pre injection Small BV superior hemisphere RPC VS Density Peripapillary was 48.71± 5.844 (min = 35, max = 5p), while the mean post injection Small BV superior hemisphere RPC VS Density Peripapillary was 50.40± 6.096 (min = 41, max = 46), in which the post injection Small BV superior hemisphere RPC VS Density Peripapillary was higher than pre-injection Small BV superior hemisphere RPC VS Density Peripapillary by 1.78. The all-superior hemisphere RPC vessel density peripapillary showed no statistically significant difference between pre- and postoperative parameters. The small and all BV inferior hemisphere RPC vessel density peripapillary showed no statistically significant variance among prior to and following injection parameters.

This was in accordance with Nicolai et al. [13] who demonstrated that vessel density inside the optic disc and in the peripapillary region significantly increased after anti-VEGF management for central retinal vein occlusion (CRVO). The changes in vessel density were statistically significant compared to the unaffected fellow eye. Analyzing the papillary and peripapillary regions may provide useful insights into microvascular changes in CRVO patients.

Elnahry et al. [14] reported significant decreases in various measures of macular perfusion (vascular density, skeleton vascular density, fractal dimension) in both the 6x6 millimeters and 3x3 millimeters macular areas after three intravitreal bevacizumab injections for diabetic macular edema. Significant increase in the foveal avascular zone (FAZ) after the injections. Significant improvement in visual acuity (18.5% decrease in Log MAR) and decrease in parafoveal thickness (5.6%) after the injections.

The association between acute intraocular pressure rise and the subsequent reduction in Optic Nerve Head perfusion after an intravitreal injection and their influence on long-term tissue alterations remains unclear. Several investigations have stated conflicting results about the association between intravitreal injections and peripapillary RNFL thinning. A meta-analysis by Shin et al. [15] determined that there was no correlation among antivascular endothelial growth factor injections and RNFL thickness when combining all data. Nevertheless, when two investigations have been separately examined, there did seem to be proof that repeated antivascular endothelial growth factor injections have been related to RNFL loss. It is interesting to document that most published research has examined eyes with a mean of not more than seven total intravitreal injections. Wen et al. [16] reported that Correlations among the escalation of intravitreal antivascular endothelial growth factor injections & maintained increases in intraocular pressure and diminished outflow facility have been observed following the eyes had received a minimum of twenty-nine and twenty injections, correspondingly. The influence of repeated intravitreal injections on RNFL thickness could not become manifest until a higher number of injections have been given; nevertheless, further longitudinal investigations are required superior evaluation of this.

Conclusion

Intravitreal injection of Ranibizumab significantly influences peripapillary perfusion as peripapillary superior RPC density significantly increased. Similarly, whole disc vessels density significantly increased with increased ONH perfusion as imaged on OCTA. Intravitreal anti-

VEGF injections are related to insignificant increases in intraocular pressure. The possibility of long-term tissue damage is still to be observed. Clinicians performing these injections must be aware of the results & follow-up the optic nerve in cases having antivascular endothelial growth factor injections.

Conflict of interest

None declared any conflict of interest.

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