

Optical Coherence Tomography Analysis of Macular Vessel Density and Area of the Foveal Avascular Zone after Single Dose of Anti-Vascular Endothelial Growth Factor Therapy in Eyes with Diabetic Macular Edema

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ABSTRACT

Objective: To assess the change in macular vessel density and area of foveal avascular zone treated with anti-Vascular Endothelial Growth Factor injection Bevacizumab in patients of diabetic macular edema with Optical Coherence Tomography Analysis.

Study Design: Prospective longitudinal study

Place and duration of Study: Armed Forces Institute of Ophthalmology Rawalpindi, Pakistan from Jan to Jun 2023.

Methods: Patients diagnosed with diabetic macular edema underwent complete eye examination. Optical coherence tomography analysis was done to check macular vessel density of the superficial plexus and area of foveal avascular zone after treatment with single dose of intravitreal anti - Vascular Endothelial Growth Factor Bevacizumab at baseline, two weeks and four weeks respectively.

Results: A significant reduction in the macular vessel density (MVD) of the superficial vascular plexus was observed in both the right and left eyes at the 2nd week (right eye: $45.1 \pm 0.9\%$; left eye: $45.0 \pm 1.0\%$) and at the 4th week (right eye: $44.8 \pm 0.8\%$; left eye: $44.5 \pm 0.9\%$). The foveal avascular zone (FAZ) increased significantly post-injection in both eyes.

Conclusion: Optical Coherence Tomography Analysis showed significant reduction in vessel density of the superficial vascular plexus and area of foveal avascular zone increased after a single intravitreal anti Vascular Endothelial Growth Factor (anti VEGF) Injection Bevacizumab. It enables us to follow up patients on short term basis who respond to the single dose of anti-VEGF treatment at anatomical level by early detection of changes on OCTA and to ascertain the response to the treatment.

Keywords: Anti-Vascular Endothelial Growth Factor (Anti-VEGF), Foveal Avascular Zone (FAZ), Macula Lutea, Macular Vessel Density, Optical Coherence Tomography (OCT), Retinal Vessels

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INTRODUCTION

Diabetic retinopathy is the leading cause of preventable blindness in adults¹. It is a micro angiopathy involving retinal blood vessel morphology and flow. Diabetic macular edema is the most common cause of vision impairment in patients with diabetes. Chronic hypoglycemia leads to the disruption of blood retinal barrier. An inflammatory cascade causes pericyte loss from the endothelium leading to vasculopathy and vasoconstriction which causes hypoxia, release of Vascular Endothelial Growth Factor (VEGF) and hence, edema². The intravitreal anti-VEGF is the standard of care for diabetic macular edema. Thorough management of patient is important to save vision and thus the quality of life of the patient. Different guidelines have been

made for the treatment³.

Fluorescein Angiography (FA) is the gold standard used in patients of diabetic macular edema and other retinal vascular pathologies. FA detects neovascularization and areas of ischemia, but it cannot assess the retinal capillary network and the vessel density. It is an invasive treatment and can also lead to severe anaphylactic reactions⁴. In past few years OCTA has revolutionized the imaging of retinal capillary network. It is a noninvasive modality, without using dye injections and permits three dimensional images of retinal circulation at high speed⁵. It recognizes the changes in signals from the movement of red blood cells in the blood vessels. OCTA helps in delineating the superficial and deep plexus three dimensionally as compared to FA. Vessel density was measured using AngioVue module Avanti instrument (Optovue, Inc., Fremont, CA, USA)⁶. OCTA also helps in the measuring the of area of foveal avascular zone using ETDRS grid method. The area within 1mm of

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ETDRS grid is the fovea and between 1mm to 3mm is the parafovea. However, the amount of data in relation to quantifying these parameters is less in our setup so these were the parameters which we have aimed to address in our study.

The aim of this study was to assess the change in the macular vessel density of the superficial capillary plexus and area of foveal avascular zone using OCTA after single dose of intravitreal anti-VEGF injection Bevacizumab in eyes with diabetic macular edema. Patients of diabetic macular edema requires multiple anti-VEGF injections which is a financial burden for both the patient and healthcare system. The aim of study was to anticipate the earliest response to the treatment⁷.

METHODOLOGY

This prospective longitudinal study was conducted in the Armed Forces Institute of Ophthalmology from January 2023 to June 2023. Ethical review (certificate 257 /ERC / AFIO dated 23 April 2021) was done by the worthy members of the ethical review committee. All patients signed the consent before enrollment.

A sample size of 84 was calculated using Open Epi Software online for proportion keeping pooled prevalence of Diabetic Macular edema to be 5.86%⁸.

Inclusion Criteria: Patients aged 55 years to 65 years with diabetic macular edema that was center involving more than 250 microns with visual acuity of 6/18 or less were included. Patients who were previously being administered intravitreal anti-VEGF Bevacizumab at least twice or thrice were included in the study group.

Exclusion Criteria: Patient with previous surgery, glaucoma and trauma were excluded. Vitreous hemorrhage, vitreomacular traction and significant media opacity were excluded from the study as these can lower the image quality and signal strength index. Patients receiving intravitreal Aflibercept and intravitreal Ranibizumab were also excluded from the study.

All the patients underwent complete eye examination including best corrected visual acuity, anterior segment examination, intraocular pressure assessment and indirect slit lamp ophthalmoscopy.

OCTA was performed using RTvue XR 100 Avanti instrument (Optovue, Inc., Fremont, CA, USA) using AngioVue software. For each eye 6 x 6mm scans centered on fovea were acquired. All parameters

before anti VEGF were documented. After confirmation of macular edema in patients 1.25mg Bevacizumab as an anti VEGF injection was given intra vitreally and OCTA images were taken at 02 weeks and 04 weeks post injection respectively.

Qualitative assessment of OCTA showed distorted foveal contour and disruptions in the retinal capillary network⁹. Quantitative follow up was done by vessel density. Vessel density is defined as the extent of the area of vessel with blood flow over the total macular area to be measured. The inner boundary of superficial capillary plexus was situated 3 microns beneath the internal limiting membrane and outer boundary 15 microns beneath the inner plexiform layer. The vessel density of the superficial capillary plexus was measured before and after treatment.

Foveal Avascular Zone (FAZ) is the central area devoid of blood vessel, and it maximizes the optical quality by limited light scattering. It is measured in millimeter square for analysis. Superficial reference plane was taken. Centre of the FAZ was clicked and the whole area of non-perfusion was analyzed using OCTA¹⁰. The readings were taken both before and after treatment.

Statistical analysis was done using the Statistical Package Social Sciences (SPSS version 27). Paired sample t test was utilized to compare the parameters at baseline and after anti-VEGF injection at 02 and 04 weeks respectively. Shapiro Wilk Test ($p > 0.05$) was chosen to evaluate the normal distribution of the parameters in the data set. Statistical significance was laid out at a p -value of 0.05 or less with a 95% Confidence Interval.

RESULTS

The study included a total of 84 patients with a mean age of 59.60 ± 3.05 years. The gender distribution was skewed towards male participants ($n=57$) as compared to female participants ($n=27$). 54 patients had only the right eye affected, whereas 30 patients had both eyes affected. OCTA was done in all patients at baseline and after the treatment with intravitreal anti-VEGF Bevacizumab at two and four weeks post treatment. (Table-I)

The table below shows the macular vessel density and area of foveal avascular zone before and after anti-VEGF injection. A significant reduction in the macular vessel density (MVD) of the superficial capillary plexus was observed in both the right and left eyes at

the 2nd week after anti-VEGF injection (right eye: $45.1 \pm 0.9\%$; left eye: $45.0 \pm 1.0\%$.) and at the 4th week after anti-VEGF injection (right eye: $44.8 \pm 0.8\%$; left eye: $44.5 \pm 0.9\%$) compared to baseline (right eye: $45.4 \pm 1.0\%$; left eye: $45.2 \pm 1.1\%$).

Table-I: Demographic Characteristics of Study Population affected with Diabetic Macular Edema (n=84)

		Values
Mean Age		59.60 \pm 3.05
Sex	Females	27(32.1%)
	Males	57(67.9%)
Eye affected	Both (left and right)	30(35.7%)
	Right	54(64.3%)

n: Frequency, %: Percentage, SD: Standard deviation

Additionally, the Foveal Avascular Zone (FAZ) increased significantly post-injection in both eyes. For the right eye, FAZ increased from 0.55 ± 0.03 mm at baseline to 0.63 ± 0.03 mm at the 2nd week anti-VEGF injection and 0.67 ± 0.03 mm at the 4th week anti-VEGF injection. Similarly, in the left eye, FAZ increased from 0.53 ± 0.04 mm at baseline to 0.62 ± 0.04 mm at the 2nd week and 0.66 ± 0.04 mm at the 4th week. (Table-II)

The macular vessel density in the superficial

analyzed before and after treatment with intravitreal Bevacizumab at 02 and 04 weeks respectively. On the contrary, decrease in macular vessel density of the superficial plexus after treatment was noted and the area of foveal avascular zone was slightly increased post treatment.

New advances in OCTA have helped clinicians and researchers to measure FAZ and vessel density as parameters and correlate them with disease progression in diabetic macular edema. A study showed that increased area of foveal avascular zone in patients of diabetic macular edema are poor responders to the anti VEGF treatment¹². The results of our study are consistent with the study by Parks et al., who reported an increase in the area of foveal avascular zone and decrease in vessel density indicating ischemic damage¹³.

Following repeated injections for the treatment of diabetic macular edema decrease in the macular vessel density was noticed in various studies¹⁴. Dabir et al., showed that anti-VEGF slows the progression of non-perfusion but doesn't completely stop it². The areas of non-perfusion would already be there but they could only be viewed after resolution of cystic edema. Another study by Dastiridou et al., showed that vessel

Table-II: Comparison of Parameters Before and After Single Dose of Anti-VEGF Injection At 2nd Week and 4th Week (n=84)

Parameter(s)	Baseline	2nd week	p value1	4th week	p value2
MVD right eye (superficial vascular plexus) (%)	45.40 \pm 1.00	45.10 \pm 0.90	<0.001*	44.80 \pm 0.80	<0.001*
MVD left eye (superficial vascular plexus) (%)	45.20 \pm 1.10	45.00 \pm 1.00	<0.001*	44.50 \pm 0.90	<0.001*
Right Eye (FAZ) (mm)	0.55 \pm 0.03	0.63 \pm 0.03	<0.001*	0.67 \pm 0.03	<0.001*
Left Eye (FAZ) (mm)	0.53 \pm 0.04	0.62 \pm 0.04	<0.001*	0.66 \pm 0.04	<0.001*

*p<0.05, significant, 1 Baseline vs 2nd week, 2 Baseline vs 4th week, Paired sample t test, MVD: Macular Vessel Density, FAZ: Foveal Avascular Zone

plexus and area of foveal avascular zone after 02 weeks and 04 weeks of single dose of intravitreal anti-VEGF injection of Bevacizumab was found to be statistically significant with the p value<0.05.

DISCUSSION

In this study the Optical Coherence Tomography Angiography (OCTA) findings demonstrated a significant reduction in vessel density within the superficial vascular plexus, along with an increase in the area of the foveal avascular zone following a single anti-VEGF injection. These observations highlight the utility of OCTA as a sensitive tool for short-term follow-up, enabling early detection of anatomical changes and facilitating timely assessment of treatment response in patients receiving anti-VEGF therapy. Anti VEGF therapy is a widely accepted treatment strategy for diabetic macular edema¹¹. Patients with diabetic macular edema were

density decreased after treatment with Aflibercept (p=0.002) and FAZ in the superficial plexus was unchanged¹⁵. Cheong et al., showed that vessel density and anatomical changes did not change significantly after treatment with anti-VEGF¹⁶. Qin et al., showed that after anti-VEGF injections visual acuity improved at 3 months of injection whereas the metrics of FAZ and vessel density remained unchanged¹⁷.

These studies were in contrast to our study in which the macular density decreases and FAZ increases after single dose of anti-VEGF. Administration of multiple intravitreal injections resulting in macular ischemia, non-responders to anti-VEGF treatment, smoking¹⁸ and masking of the non-perfused capillary areas with edema¹³ on OCTA could have been a contributory factor for these results. Furthermore, studies would be required by comparison of vessel densities and area of FAZ with

healthy subjects and diabetic macular edema. Studies comparing efficacy of various anti VEGF therapies,^{19,20} and comparing the parameters of the patients who have not received any intravitreal anti-VEGF injection and those who have received multiple intravitreal anti-VEGF injections would be required. Treatment responders and non-responders would be required in future for better correlation of the parameters. These OCTA parameters can be correlated with Fluorescein Angiography (FA) for more detailed overview which require more studies.

LIMITATION OF STUDY

Patients with refractory diabetic macular edema were not included in the study. This study did not include measurements of FAZ through FA. Our study was based on immediate short term outcome. A single anti VEGF i.e. intravitreal Bevacizumab was used in our study. Furthermore, OCTA requires a steady gaze as blinking affects the image quality, but this can be overcome by patience during testing, better lubrication of the eye and appropriate selection of patients.

CONCLUSION

Optical Coherence Tomography Analysis (OCTA) showed significant reduction in vessel density of the superficial vascular plexus and area of foveal avascular zone increased after a single anti-VEGF injection. It enables us to follow up patients on short term basis who respond to the single dose of anti-VEGF treatment at anatomical level by early detection of changes on OCTA and to ascertain the response to the treatment.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

JAQ & AM: Data acquisition, data analysis, critical review, approval of the final version to be published.

AK & MAM: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MN & FA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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