

# Effect of Intravitreal Bevacizumab on the Optic Nerve Head Perfusion in Patients with Diabetic Macular Edema

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## ABSTRACT

**Purpose:** To find out the effect of Intravitreal Bevacizumab on optic nerve head perfusion using Ocular Coherence Tomography Angiography (OCTA) in patients with diabetic macular edema (DME).

**Study Design:** Interventional case series.

**Place and Duration of Study:** Ophthalmology Department, Mayo Hospital, Lahore from June 2018 to January 2020.

**Methods:** In this study 57 eyes of patients fulfilling the inclusion criteria were selected from the outpatient department. After informed consent, detailed history and ocular examination was performed. Baseline OCTA was done in all cases. The patients received intravitreal Bevacizumab (1.25 mg in 0.05 ml). OCTA was repeated three weeks after injection. Both the pre and post injection ONH perfusion was compared and analyzed using SPSS. Demographic characteristics like age and gender were calculated. Paired sample t-test was applied to check the significance of difference between pre and post injection values. P-value of < 0.05 was considered significant.

**Results:** There were 16 (28.1%) males and 41 (71.9%) females. Mean age of the patients was  $53.54 \pm 7.00$  years. Pre injection blood flow was 56.11 and post injection was significantly reduced to 52.69. The mean difference between was 3.423 and confidence interval of the difference was (2.5755-4.2701). P-value 0.000 was < 0.05 which showed significant reduction in perfusion of ONH.

**Conclusion:** Intravitreal Bevacizumab decreases the optic nerve head blood flow and should be used with care in patients having reduced blood flow states and also in patients with advanced glaucomatous optic neuropathy.

**Key Words:** Diabetic macular edema, Intravitreal Bevacizumab, Optical coherence tomography angiography, Diabetic Retinopathy, Optic nerve head, Vascular endothelial growth factor.

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## INTRODUCTION

Diabetic macular edema (DME) is one of the major complications causing visual loss in Diabetic Retinopathy.<sup>1</sup> It is characterized by occlusion and loss of normal macular capillary network.<sup>2</sup> Intravitreal anti-

vascular endothelial growth factor (anti-VEGF) has been commonly used for the treatment of diabetic macular edema. Off-label intravitreal Bevacizumab is the commonest drug in this regard. Anti-VEGF injections are used to treat various retinal vascular disorders including diabetic macular edema.<sup>3</sup> These agents not only affect DME but also have influence on Optic nerve head blood flow.<sup>4,5</sup> Optical coherence tomography angiography (OCTA) is one of the latest techniques that can be used noninvasively to detect perfusion of the optic nerve head at the capillary level.<sup>6,7</sup> OCTA allows to study retinal microvasculature by calculating the difference

between a static tissue (vessel) and a dynamic one (red blood cells).<sup>8</sup> Red blood cells movement in the retinal capillaries is used as an intrinsic contrast medium to generate flow imaging and it is independent of the direction of movement of cells, with the removal of all static (structural) information by the software.<sup>9</sup>

This study was conducted to evaluate the changes in the ONH perfusion before and after an intravitreal injection using OCTA in patients having diabetic macular edema (DME) with moderate to severe non-proliferative diabetic retinopathy (NPDR).

### METHODS

This interventional case series was conducted from June 2018 to January 2020 in Ophthalmology Department of Mayo Hospital, Lahore. Fifty seven patients of 20 to 60 years of age, with moderate and severe non-Proliferative Diabetic Retinopathy. NPDR with DME, no previous history of any other ocular disease, no previous ocular surgery or trauma were included. Patients with Proliferative Diabetic Retinopathy (PDR), any other ocular pathology,

previous history of treatment for any type of diabetic retinopathy were excluded.

After approval from ethical review board, the study was started and informed consent was taken from every patient. Complete history and examination including vision, intra ocular pressure (IOP), refraction, detailed anterior and posterior segment evaluation were performed in every patient. OCTA was performed to measure the blood flow of ONH. All patients received intravitreal Bevacizumab (1.25 mg in 0.05 ml), 3.5mm behind the limbus in the infrotemporal quadrant, using all the standard protocols in the hands of a single experienced surgeon. OCTA was repeated after three weeks. Scanning protocol was 200x200 sampling points over 6x6 mm<sup>2</sup> area centered on optic disc to check the changes in blood flow of ONH through vessel area density. Pre and post injection scans were compared and analyzed using SPSS. Demographic characteristics like age and gender were calculated. Paired sample t-test was applied to check the significant difference between pre and post injection perfusion. P-value of < 0.05 was considered significant.

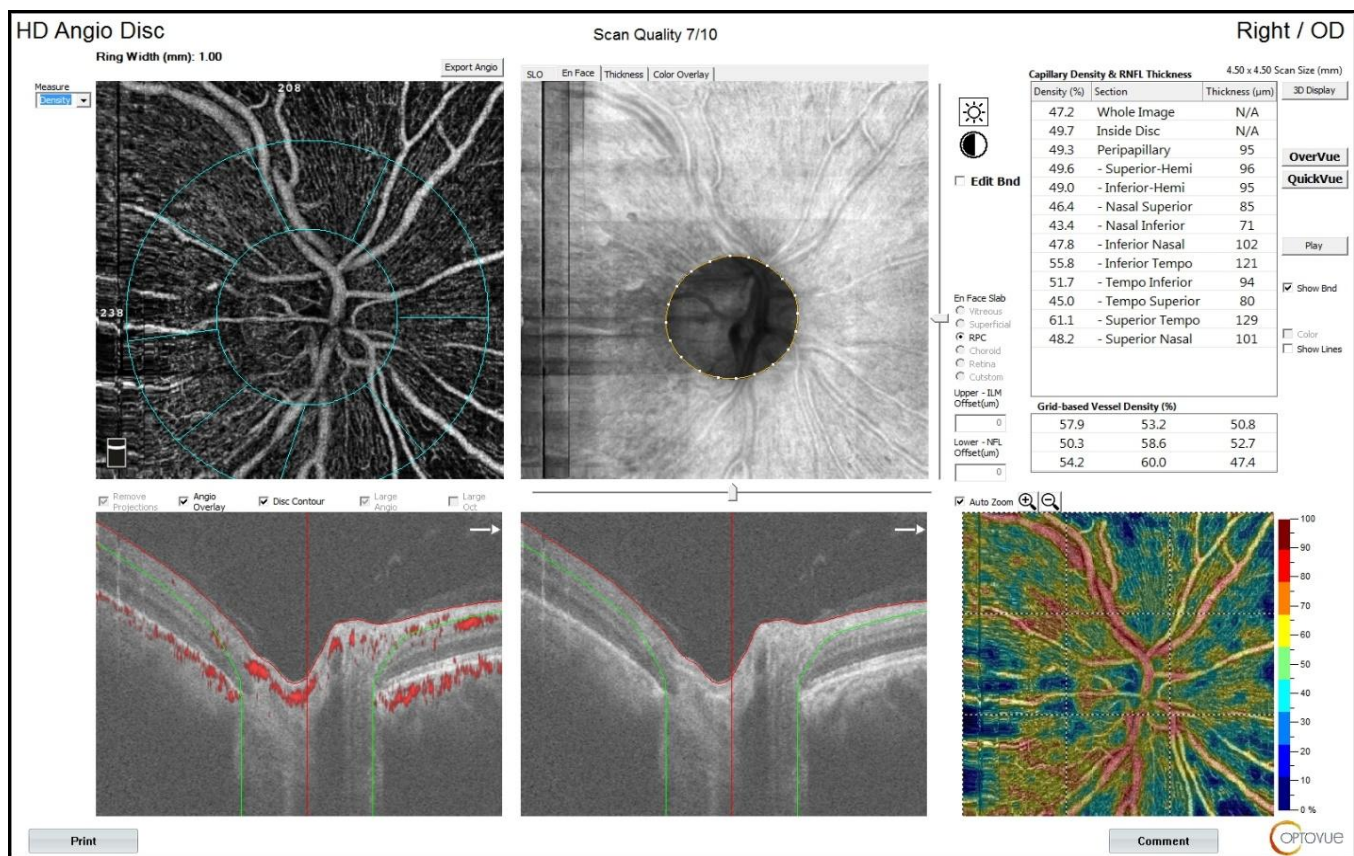


Figure 1: OCTA Scan showing the blood flow at optic nerve head.

## RESULTS

There were 16 males (28.1%) and 41 (71.9%) females. Mean age was  $53.54 \pm 7$  years. In this study, out of 57 eyes 50 eyes had decrease in ONH perfusion, five eyes had slight increase and two eyes showed no change in perfusion. The mean difference between pre and post injection perfusion was 3.423 and confidence interval of the difference was (2.5755 – 4.2701). P-value was 0.000 which is  $< 0.05$  and showed the significant difference between pre and post injection perfusion of ONH (Table 1).

**Table 1:** Pre and Post Avastin Perfusion of ONH.

	Mean	Mean Difference	Confidence Interval	P-value
Pre-Avastin	56.11	3.423	2.5755-4.2701	0.000
Post-Avastin	52.69			

## DISCUSSION

This study showed a statistically significant decrease in ONH perfusion after intravitreal injection of Bevacizumab. The results correlate with another study which showed transient effect on optic nerve perfusion in response to IOP increase due to intravitreal injection.<sup>10</sup> However, our results showed decreased perfusion of ONH even after three weeks.

Numerous studies are available showing the effect of intravitreal anti-VEGF on chorioidal circulation and retinal circulation using different techniques but our study just shows its effect on ONH and uses OCTA to measure the blood flow.<sup>11,12,13</sup> Fukami et al. studied the effects of Ranibizumab injection in eyes with macular edema in retinal vein occlusion and found that the injection led to vasoconstriction of retinal vessels and reduction of retinal blood flow.<sup>14</sup> Similarly, Sugimoto et al. assessed the effects of unilateral intravitreal Ranibizumab on ocular circulation of patients treated for DME. They showed a decrease of mean blood flow rate of ONH after treatment in the affected eye, but not in the fellow eye which was untreated.<sup>15</sup>

Nitta et al. showed a comparison between DME patients and patients with Branch retinal vein occlusion (BRVO) and concluded that mean blood flow did not change significantly after intravitreal Bevacizumab in the BRVO group, on the other hand in DME group it had decreased.<sup>16</sup> In another study, intravitreal injection of bevacizumab was seen to

significantly affect the ocular hemodynamic parameters of both the injected and the un-injected fellow eyes with neovascular age-related macular degeneration.<sup>17</sup>

We studied the effect of a single anti-VEGF injection in DME. Similarly there are other studies showing decrease in retinal arteriolar, choroidal and ONH perfusion after intravitreal anti-VEGF.<sup>18,19</sup>

Contradictory to these there is evidence of short-term reduction in perfusion only in the treated eye which was independent from IOP, indicating a direct pharmacological effect. No changes in choroidal perfusion were observed during the first 45 min after the injection.<sup>20</sup> Whether this significant decrease in ONH perfusion as imaged on OCTA, leads to any long-term tissue damage remains to be seen. However, clinicians performing these injections should be well aware of these findings and carefully monitor the optic nerve in patients undergoing anti-VEGF injections.

Limitations of this study are small sample size and short follow up. The additive effect of repeated injections could be measured in case of longer follow ups. Moreover, a comparison with other anti-VEGF drugs such as Ranibizumab and Aflibercept could disclose other ocular blood flow changes.

## CONCLUSION

Intravitreal Bevacizumab decreases the optic nerve head blood flow and should be used with care in patients having reduced blood flow state especially in patients with advanced glaucoma.

**Conflict of Interest:** Authors declared no conflict of interest.

## Ethical Approval

The study was approved by the Institutional review board/Ethical review board (COAVS: 114/2022).

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### **Authors' Designation and Contribution**

Nida Usman; Consultant Ophthalmologist: *Designs, Data acquisition, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review.*

Muhammad Ali Haider; Consultant Ophthalmologist: *Concepts, Design, Literature search, Data analysis, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review.*

### **DISCLAIMER**

*This research study was conducted at KEMU and all authors were present in the said place during the conduct of the study.*

