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Original Article

OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY AFTER RANIBIZUMAB TREATMENT FOR DIABETIC MACULAR EDEMA

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Abstract

Purpose: *of this study is to assess changes and to assess ischemia that may occur post. Injection using OCT and OCTA and its relation with BCVA.* ***Methods:*** *prospective, observational, cohort study with a total 49 eyes were enrolled in the study to evaluate changes in central macular thickness, visual acuity, foveal avascular zone and vascular density following intravitreal injection of ranibizumab used in patients diagnosed with central involving diabetic macular edema.* ***Results****: There was highly significant improvement in BCVA (p <0.0001). As regard macular thickness there was significant reduction of macular thickness (p<0.0001). There is high relation between IS-OS integrity, DRIL and BCVA. We found improvement of IS-OS line post. Injection as regard FAZ there was non-significant enlargement of FAZ post. Injection (p =0.16). Vascular density in superficial capillary plexus was statistically highly significant (decreased) when we compare before and after injection as a whole density, fovea, parafovea &perifovea while it is not significant changes when we compare values between (1&6 m) and between (3&6m). While vascular density in deep capillary plexus It was statistically significant (reduction) only in fovea and perifoveal superior (p= 0.02) while non-statistically significant reduction of vascular density elsewhere.* ***Conclusion:*** *Our result concluded that intravitreal injection of ranibizumab is an influential treatment for diabetic macular edema with minimal ischemia and minimal effect on macular perfusion. Anatomical and functional factors other than central macular thickness are also related to best corrected visual acuity. So, OCT and OCTA are very helpful during follow -up cases with DME to assess macular thickness, inner and outer retinal integrity, degree of macular ischemia and any complication as ERM that may result from injection.*

Keywords: *Ranibizumab, OCT, OCTA, CMT, BCVA*.

1. Introduction

Diabetic retinopathy (DR) is a major cause of blindness in developed countries [1]. The incidence of DR continues to increase all over the world [1]. the most common cause for vision affection in patients with diabetes milletus is diabetic macular edema (DME) [2]**.** Its treatment involves focal or grid laser which was the main treatment of DME as shown by the Early Treatment Diabetic Retinopathy Study (ETDRS) since 1985 and/or anti – vascular endothelial growth factor. They decrease the risk by 50% for significant vision loss, but vision loss never stops

and improvements in BCVA are rare [3]. Many investigations are necessary for diagnosis and follow-up of DR. Fluorescein angiography (FA) is now the most useful and used investigatory tool [4]. But FA is considered invasive tool as it requires injection of fluorescein dye intravenously which may cause many risks as vomiting, nausea, itching and even urticaria, and in rare cases may cause anaphylaxis [4]**.** Also, detecting ischemia is another drawback. As quantification of perfusion by FA may be difficult due to masking effect of leakage and hemorrhage and may affect our ability to assess accurately the deep retinal capillary plexus [5]. Optical coherence tomography angiography (OCTA) is a recent technique which helps us to visualize the retinal microvasculature and considered a non-invasive technology in the judgement of perfusion. It enables us to segment retinal vasculature to visualize individual retinal vasculature separately. (superficial and deep capillary plexus) [6].

2. Patients and Methods

2.1. *Study design*

Prospective observational cohort study.

2.2. *Subjects*

The study included 49 eyes. At first the study enrolled 65 eyes with center involving diabetic macular edema; they were defined according to early treatment diabetic retinopathy study group (ETDRS). But 9 of them missed their follow-up schedule. And 7 were excluded as they have non-measured FAZ or macular density at any time during their follow-up. We follow treat and extend (TAE) protocol. We start with 3 injections with 0.5 mg ranibizumab (0.1ml) one per month while the macular edema resolution is monitored by means of OCT and intervals are extended by 2-4 weeks. Once the patients longest intervals are found, he undergoes fixed interval injections. Data was collected between august 2020 and December 2022 at Sohag Ophalmology Investigation Center and Sohag University Hospital. All participants were informed about the investigations that will be done to them. Approval from ethical committee of Sohag Faculty of Medicine was obtained. *Inclusion criteria*: Patients with clinically significant central involving macular edema. On OCT (central macular thickness > 250 Mm). Those patients were treated with anti-VEGF by 3 injections with a dose of 0.5 mg ranibizumab (0.1ml) at baseline and every 4 weeks. We take in consideration that all participants had good quality scans obtained by OCT and OCT angiography. *Exclusion criteria:* **1)** Patients with uveitis, glaucoma not controlled medically. **2)** Patients with vitreous opacities or hemorrhages. **3)** tractional RD threaten the macula. **4)** Eyes with media opacity significant enough to affect the images quality. **5)** Eyes with marked image distortion or significant artifact prevent measurement of the FAZ and vessel density accurately. *Ethical consideration and written informed consent*: an approval of the study was obtained from Sohag University Academic and Ethical Committee. And consent for acceptance of the procedure was obtained from all patients.

2.3. *Methods*

2.3.1. Patient evaluation

Each participant was subjected to full history, Comprehensive ophthalmological examination, including refraction, best-corrected visual acuity (measured by Sne-

llen`s or Decimal notation scale then all converted to decimal), IOP measurement using Goldman applanation tonometer, ant. Segment examination by slit lamp biomicroscopy and examination of fundus by auxiliary lens and\or indirect ophthalmoscope. Examination of the macula was done by Swept source OCT (SS- OCT) and by Optical coherence tomography angiography.

2.3.2. Methods of study

OCT was performed using swept source OCT (SS-OCT).

- **OCT parameters**

1) Central macular thickness. (According to ETDRS) **2)** Parafoveal thickness in 4 quadrants. (According to ETDRS). **3)** Perifoveal thickness in 4 quadrants. (According to ETDRS). **4)** Integrity of outer retinal layers (IS-OS ellipsoid layer, ELM integrity and interdigitation zone): if it disrupted or intact or absent. It is important to be evaluated in cases of DME. **5)** RPE integrity. **6)** Organization of inner retinal layers and detection of disorganization (DRIL). **7)** Post maneuvers we look for development of complications as ERM and scarring.

- **OCT angiography**

Was performed using an RTVue XR Avanti with Angio Vue software (Optovue, Inc., Fremont, California, USA). For each eye, a 6 X 6 -mm scan centered on the fovea. Automated OCT segmentation will be Performed using the Angio-Vue module.

- **OCTA parameters**

1) Vessel density (superficial and deep capillary plexus). **2)** 2- FAZ area. **FAZ** the area of the central fovea in which there is no vessels. FAZ size was calculated automatically using the software of the machine. **Vessel densities:** Vessel density is defined as the proportion of the measured area occupied by blood vessels in both deep vascular plexus (DVP) and superficial vascular plexus (SVP).

- **Follow-up with**

1) BCVA (best corrected Visual acuity). **2)** OCT parameters. **3)** OCT angiography parameters. Follow-up was scheduled to be at one month, three months and 6 months.

2.4. *Statistical analysis*

Using SPSS version 18 we analyzed the data. Comparison was made between pre and post treatment follow up data at 1, 3 and 6 months (repeated measure ANOVA) RMANOVA test. Sphericity were examined using Mauchly's Test of Sphericity. Bonferroni post hoc test to examine the difference at each time point. The different time points used as within subject factors. Student t test was used to compare injection and laser group. Chi square test used for categorical data. P value was considered significant if it was < 0.05.

3. Results

3.1. *Criteria of studied group*

1) Age & gender: included 49 eyes totally with 27 eyes of 18 females and 22 eyes of 17 males with mean age 56.20± 10.09 years old, tab. (1). **2) IS-OS ellipsoid layer and external limiting membrane integrity:** disruption of ELM was detected in 10 eyes (20.5%) and disruption of IS/OS in 18 eyes (35%). But no eye with absent IS-OS, tab. (2). **3) DRIL** (disorganization of

inner retinal layers): 9 eyes (18.5%) have DRIL. We found that mean BCVA in those with DRIL is 0.12 while in those without DRIL is 0.19, tab. (2).

Table 1: Demographic criteria studied group.

Variable		Injection group N=49
Age/years	* Mean ± SD * Median (range)	56.20±10.09 57 (42:77)
Gender	* Female * Male	27 (55.10%) 22 (44.90%)
Eye	* OD * OS	27 (55.10%) 22 (44.90%)

Table 2: Criteria of OCT parameters in studied group

Variable	Frequency	Percentage
Disturbed IS-OS	18	36.7%
Disturbed ELM	10	20.5%
DRIL	9	18.5%

3.2. *Parameters which were studied*

In all following parameters: **a) P value** for repeated measures**. b) Pairwise comparison** P1 compared before & 1m, P2 compared before &3ms, P3 compared before & 6ms, P4 compared 1m &3ms, P5 compared 1m & 6ms, P6 compared 3ms & 6ms.

1) Changes in BCVA

Visual acuity pre-injection mean was (0.19±0.06) in decimal which improved to (0.26±0.07) after 6m. follow-up after injection which is highly significant change. Changes in visual acuity before and after injection continue till the 3rd month of follow-up. But there was non-significant improvement when we compare visual acuity between 3rd and 6th months after injection. With 71.5% (35 eyes) have improvement in their visual acuity, 22.5 % (11 eyes) stabilized visual acuity & 6% (3 eyes) have been deteriorated, tab. (3).

Table 3: Changes in visual acuity before and after injection.

Variable	Before injection	Post injection (1 month)	Post injection (3 month)	Post injection (6 month)	P value
VA Mean ± SD Median (range)	 0.19±0.06 0.16 (0.13:0.32)	 0.24±0.07 0.25 (0.13:0.40)	 0.26±0.07 0.25 (0.13:0.40)	 0.26±0.07 0.25 (0.13:0.40)	 <0.0001
P1<0.0001, P2<0.0001, P3<0.0001, P4=0.002, P5=0.002, P6=1.00					

2) IS -OS ellipsoid layer and ELM integrity

We found improvement of IS-OS and ELM integrity with 12 eyes still with disturbed IS-OS at 6m. follow-up while it was 18 eyes at baseline. And 7 eyes with disturbed ELM at 6m. follow-up from 10 eyes at baseline. With percentage of disturbed IS-OS decrease from 36.5% at baseline to 24.5% at 6m.at follow-up period. While percentage of disturbed ELM decrease from 20.5% to 14 %, tab. (4). We correlate their integrity with BCVA. Those with intact IS-OS and those with disrupted IS-OS groups were different significantly in BCVA at baseline which was 0.19, 0.12 while after 6 months it was 0.26 and 0.16. Results were similar for ELM groups. Also BCVA was significantly different in those with intact ELM and those with disrupted ELM, at baseline it was 0.2 & 0.12 and after 6 months it was 0.32& 0.25, tab. (5).

Table 4: Outer retinal layers integrity before and after injection:

	At baseline	After 6months follow-up
Disrupted IS-OS	18 eyes	12 eyes
Disrupted ELM	10 eyes	7 eyes

Table 5: Outer retinal layers integrity and its relation with BCVA

	Mean BCVA at baseline	Mean BCVA at 6m.
Intact IS-OS layer	0.19	0.26
Disrupted IS-OS layer	0.12	0.16
Intact ELM	0.2	0.32
Disrupted ELM	0.12	0.25

3) DRIL

6 eyes still have DRIL**.** With mean BCVA at 6m. in those with DRIL was 0.16 while mean BCVA in those without DRIL was 0.29

4) Complications

Regarding this point (*Complications*) No eyes develop ERM Post injection & no eyes have major complication as endo-phthalmitis.

5) Macular thickness

There is highly statistically significant improvement in macular thickness before and after injection at all periods of follow up (1, 3 & 6), tab. (6).

Table 6: Macular thickness before and after injection

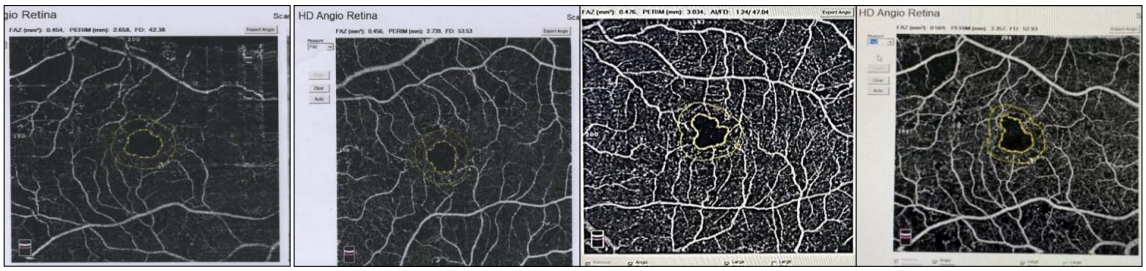
Variable	Before injection	Post injection (1 month)	Post injection (3 month)	Post injection (6 month)	P value
CMT					
Mean ± SD	424.43±120.45	268.39±84.39	259.08±72.47	257.76±72.26	<0.0001
Median (range)	395 (295:810)	235 (177:533)	239 (175:460)	230 (176:460)	
P1<0.0001, P2<0.0001, P3<0.0001, P4=0.007, P5=0.002, P6=0.001					

6) FAZ

Statistically non-significant changes occur in FAZ when we compare FAZ area before and after injection during period of follow-up at 1.3 &6months, tab. (6) & fig. (1).

Table 7: FAZ before and after injection

Variable	Before injection	Post injection (1 month)	Post injection (3 month)	Post injection (6 month)	P value
FAZ					
Mean ± SD	0.42±0.19	0.44±0.19	0.44±0.18	0.46±0.20	0.16
Median (range)	0.37 (0.19:1.21)	0.38 (0.21:1.02)	0.39 (0.23:1.01)	0.40 (0.23:1.12)	
P1=0.56, P2=0.25, P3=0.23, P4=0.16, P5=0.15, P6=0.45					



a b c d

Figure 1: OCTA images of female patient 61 y. old reveal FAZ before and after injection; **a.** at baseline, **b.** at 1st m., **c.** at 3rd m **d.** at 6th m. of follow -up.

3.3. *Superficial vascular density at different time in injection group*

Vascular density in superficial capillary plexus was statistically highly significant (decreased) when we compare before and after injection as a whole density. And statistically significant in fovea, parafovea &perifovea while it is not significant changes when we compare values between (1&6 m) and between (3 & 6 m), tab. (8).

Table 8: Vascular density in superficial capillary plexus.

Variable	Before injection	Post injection (1 month)	Post injection (3 month)	Post injection (6 month)	P value
Whole density Mean ± SD Median (range)	42.52±5.26 41.9 (34.6:53.1)	41.27±5.06 41 (33.2:50.6)	41.11±5.06 41 (33.1:50.4)	40.86±5.08 41.1 (32.9:50)	<0.0001
P1=0.001, P2<0.0001, P3=0.001, P4<0.0001, P5=0.85, P6=1.00					
Fovea Mean ± SD Median (range)	20.86±13.41 18.8 (0.20:49.6)	18.89±12.72 18 (2.3:46.6)	18.82±12.68 18 (2.4:46.6)	18.92±12.79 17.7 (2.3:46.5)	0.001
P1=0.003, P2=0.002, P3=0.06, P4=0.03, P5=1.00, P6=1.00					
Parafovea Mean ± SD Median (range)	39.76±7.34 41.1 (18.1:52.1)	38.95±7.11 40.4 (17.9:50.8)	38.81±7.17 40.4 (17.2:50.6)	38.63±7.20 40.5 (17:50.5)	0.002
P1=0.02, P2=0.006, P3=0.03, P4<0.0001, P5=1.00, P6=1.00					
Perifovea Mean ± SD Median (range)	43.85±6.14 43.2 (30.1:54.3)	42.54±6.11 42.1 (29.8:53.6)	42.61±5.82 41.9 (33.1:53.5)	42.47±5.86 41.4 (33:53.3)	0.001
P1<0.0001, P2=0.01, P3=0.04, P4=1.00, P5=1.00, P6=1.00					

3.4. *Deep vascular density at different time in injection group*

It was statistically significant (reduction) of vascular density in deep capillary plexus only in fovea and while non-statistically significant reduction of vascular density elsewhere, tab. (9).

Table 9: Vascular density in deep capillary plexus.

Variable	Before injection	Post injection (1 month)	Post injection (3 month)	Post injection (6 month)	P value
Whole density Mean ± SD Median (range)	40.48±5.55 42.2 (25.6:48.8)	40.69±5.53 41.6 (25.1:51.6)	40.57±5.52 41.5 (25:51.5)	40.38±5.56 41.2 (24.5:51.3)	0.74
P1=1.00, P2=1.00, P3=1.00, P4<0.0001, P5=1.00, P6=1.00					
Fovea Mean ± SD Median (range)	32.73±14.45 35.3 (4.9:63.3)	30.57±13.37 33 (5.1:61.2)	30.39±13.20 32.7 (6.1:61.1)	30.21±13.12 32.5 (6:60.5)	0.02
P1=0.23, P2=0.15, P3=0.10, P4=0.29, P5=0.03, P6=0.20					
Parafovea Mean ± SD Median (range)	43.41±7.07 44.2 (26.6:55)	43.19±6.98 44.6 (26:53.5)	43.05±7.02 44.5 (25.7:53.4)	42.86±6.99 44.4 (25.6:53.2)	0.48
P1=1.00, P2=1.00, P3=1.00, P4<0.0001, P5=1.00, P6=1.00					
Perifovea Mean ± SD Median (range)	41.76±5.98 41.5 (25.2:50.2)	41.41±6.09 43.2 (24.8:49.2)	41.22±6.21 43.1 (24.6:49.1)	41.08±6.20 43.2 (24.5:48.9)	0.26
P1=1.00, P2=1.00, P3=1.00, P4=0.03, P5=1.00, P6=1.00					

4. Discussion

In our study, BCVA before and after injection of anti-VEGF has been improved, except during period (3 & 6 m) of follow-up as the improvement become stationary after 3rd month. This is in agreement with Tawfek et al study which found that the mean BCVA in decimal among patients achieve an improvement 25.0% this was strongly statistically significant [7]. In our study we assessed macular thickness before and after injection and we found that macular thickness decreased during follow-up (1 & 3 m.) which was statistically significant (p<0.0001). But between 3- and 6-months during follow-up macular thickness remains stationary with no significant increase or decrease. Many studies agree with our study as Elbeheiri, et al study there was highly significant improvement in the visual acuity (VA) and reduction in the macular thickness significantly in the studied cases after one month and after three months when compared with the pretreatment value (P<0.001) after ranibizumab injection [8]. This also in agreement with Ebneter et al study which found that the mean BCVA improvement at 12 months was 6.2 ETDRS letters, and central retinal thickness decre-

ased. In the central subfield, also asignificant reduction of thickness for all layers ($P < 0.001$) after ranibizumab injection [9]. In our study, we studied the change in IS-OS & ELM integrity after injection and correlated the integrity with changes in BCVA and we found that the cases with intact IS-OS line and ELM from the start showed better change in BCVA than cases with disturbed outer retinal layers. Also, injection have rule in the improvement of their integrity with percentage of disturbed IS-OS decrease from 36.5% at baseline to 24.5% at 6 m. at follow-up period. While percentage of disturbed ELM decrease from 20.5 % to 14%. This agreed with Sherif Zaki Mansour, et al study who found that lower visual acuity after macular edema improvement in cases with more outer retinal layers damage at the time of diagnosis DME, and intact outer retinal layers is an important factor which greatly affect the final visual acuity [10]. This was studied by Tomoaki Murakami, et al study who found that the IS/OS line represents the anatomy and function of the photoreceptors in vivo. The length of disruption or absence of IS/OS line also affect visual acuity. The ELM line is also an important factor, and its disruption is associated with visual impairment in DME [11]. Ilkay Kilic Muftuoglu, et al study agrees with our study that the final visual acuity was also correlated with ELM damage. Their study found that damage of ELM was the most important predictor for final vision then baseline visual acuity and lastly Hb1Ac [12]. As regarding DRIL, we found that eyes with disorganization of inner retinal layers have worse BCVA at their first visit (at baseline). This agreed with Ilkay Kilic Muftuoglu, et al study that found that there are multiple factors that may affect the visual outcomes such as inner retinal layers disorganization or developpment of ischemic maculopathy after DME resolution [12]. Also agreed with M. Luís, et al study that found that DRIL was related to the baseline BCVA and also affect both CMT and BCVA end results [13]. In our study there was no significant changes in FAZ changes were non-statistically significant during all period of follow-up. This was in agreement with Mirshahi, et al study which found that at the short-term follow-up after intravitreal injection of anti-VEGF, the FAZ area remained the same [14]. And also, in agreement with Falavarjan et al study which found that FAZ area after only single anti-VEGF dose were statistically unaffected [15]. That was in contrast to Nazmiye Erol, et al study which found that FAZ area were enlarged significantly (P= 0.012) after anti-VEGF intravitreal injection for diabetic macular edema [16] but after division of patients into 2 groups, they found that enlarged FAZ was statistically significant in cases with mild diabetic retinopathy, but not significant in more than mild DR. also they use intravitreal bevacizumab as anti-VEGF while in our study we use ranibizumab. Conflicting result was found in other studies as Tawfek, et al study which found that FAZ areas enlarged significantly in diabetic patients [17]. This confliction may be due to that there are many factors may play role on macular perfusion. As improvement of retinal perfusion after anti-VEGF injection by the reversal of leukocytosis, or worsening of retinal perfusion after VEGF inhibition by induction of vasoconstriction of the retinal vessels may be due to nitric oxide inhibition which occurs with VEGF inhibition. In our study we measured macular perfusion in both superficial and deep capillary plexus, and we found that superficial capillary plexus was significantly decreased as a whole density, fovea, parafovea specially parafoveal nasal & perifovea. But there was significant reduction during the first 3 months while after that (during period of 3-6 m. of follow -up) changes were non-statistically significant. There were no statistically significant changes in vascular density in deep cap-illary plexus before and after intravitreal anti-VEGF injection and during whole period

of our follow-up. So, from that we can conclude that intravitreal injection of ranibizumab does not affect FAZ, vascular density in deep capillary plexus but has more effect affect (a significant reduction) of vascular density in superficial capillary plexus. So, we can conclude that intravitreal injection has more effect on superficial capillary plexus than on deep capillary plexus. Małecka, et al. study found vascular density for the whole macular area in 3×3 mm scans not differ in all presented cases [18]. That was not the same with Elnahry, et al. study which found that VD in the SCP, and DCP in the 6×6 mm OCTA scan decreased significantly, that represent that anti-VEGF injections associated with reduction in macular perfusion. This difference may be due to smaller study group of their study (only 26 eyes were included in Elnahry, et al. study) and they also use bevacizumab not ranibizumab [19]. Also, Elnahry, et al. study found that the FAZ area enlarged, the VD of the SCP and DCP were reduced in the 6×6mm OCTA scans after the injections which were all statistically significant (p <0:05) [20]. This difference from our study may be due to difference in severity of diabetic retinopathy and diabetic edema.

5. Conclusion

Our result concluded that intravitreal injection of ranibizumab is an influential treatment for diabetic macular edema with minimal ischemia and minimal effect on macular perfusion. Anatomical and functional factors other than central macular thickness are also related to best corrected visual acuity. So, OCT and OCTA are very helpful during follow -up cases with DME to assess macular thickness, inner and outer retinal integrity, degree of macular ischemia and any complication as ERM that may result from injection.

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