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Research Article

Multifocal Electroretinogram in Cystoid Macular Odema after Intravitreal Injection of Triamcinolone Acetonide

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Abstract

Purpose: To review the efficacy of intravitreal injection of triamcinolone acetonide in cystoid macular oedema (CMD) by multifocal electroretinogram (MF-ERG) and optical coherence tomography (OCT) and to correlate between MF-ERG and OCT.

Subjects and Methods: This study included patients with cystoid macular oedema (which is due to diabetes, pseudophakia and branch retinal vein occlusion). Patients underwent complete ophthalmological examination, OCT, MF-ERG before and after intravitreal injection of 4 mg of triamcinolone acetate.

Results: The Study included sixty patients (60 eyes in 60 patients) with CME, 42 eyes due diabetes, 12 eyes due to retinal vein occlusion and 6 eyes due to cataract extraction with intraocular lens. There were reduction of retinal thickness of the macula by OCT and increase of the amplitude and reduction of latencies of MFERG after intravitreal injection of triamcinolone acetate. There were negative correlation between MFERG amplitude and OCT retinal thickness.

Conclusion: IVTA improve retinal function and decrease macular thickness with few complications.

Keywords: *Cystoid Macular Oedema (CMO); Multifocal Electroretinogram (MF-ERG); Optical Coherence Tomography (OCT)*

Introduction

Cystoid macular oedema (CMO) is resulted from cystic accumulation of intraretinal fluid in the outer plexiform and inner nuclear layers of the retina as a result of the breakdown of the blood-retinal barrier [1-3].

CMO occurs in different pathological conditions as intraocular inflammation, central or branch retinal vein occlusion, diabetic retinopathy and following cataract extraction [4].

Triamcinolone acetonide is effective in the management of cystoid macular edema [3] because it suppresses inflammation, decrease extravasation of fluid from leaking blood vessels, inhibits fibrovascular proliferation, and down regulates production of VEGF [5].

Multifocal Electroretinogram is a non-invasive technique that allows mapping of hundreds of discrete retinal locations [6].

Optical coherence tomography is a non-invasive, non-contact imaging allowing quantitative measurements of retinal volume [7].

Aim of the Study

The aims of the study were to review the effectiveness of IVTA in treatment CME and to correlate between OCT and MFERG.

Subject and Methods

The study included patients attending Mansoura Ophthalmic Center and suspected to have macular edema between January 2018 to January 2020. They undergo complete ophthalmological examination.

Inclusion criteria were: Patients with diabetic cystoid macular edema as confirmed by OCT with macular thickness(MT) more than 300 µm, Patients with branch retinal vein occlusion with MT > 260 µm and the duration of macular edema is more than 3 months, Pseudophakic Patients with CME more than three months unresponsive to topical non-steroidal anti-inflammatory medications or topical corticosteroid.

Exclusion criteria were: Glaucoma, *vitro*-retinal pathology such as epi-retinal membrane or *vitro*-macular traction, diffuse or central retinal degeneration, history of laser photocoagulation, Recurrent CMO.

In this study, patients were injected intravitreally by triamcinolone acetonide. Topical antibiotic eye drops were prescribed three days before IVTA injection.

The injection was consisted 0.1 ml (4 mg) of a commercially available suspension of triamcinolone acetonide (Amcinol 40 mg/ml, Sigma Company).

Technique of IVTA: It was performed at the operating theater using aseptic technique. Topical anesthetic drops were instilled, cleaning of the injection site with 5% povidone-iodine. The injection was performed using a 27-gauge needle inserted through the pars plana 4mm posterior to limbus in the infro-temporal quadrant. Paralimbal paracentesis was done to reduce the intra ocular tension.

Following the injection, an antibiotic ointment was administered and the eye was patched overnight. Topical antibiotic eye drops were instilled for three days after IVTA.

The patients were monitored for injection-related complication 1, 3, 7 days, 1 month, 2 months and 3 months after injection.

The anatomical and functional responses to treatment were followed up at 1month, 2months and 3months after IVTA injection by OCT and MF-ERG.

OCT: Was performed with the 3-dimensional OCT-1000 (Topcon Corporation, Tokyo, Japan). OCT measurements were performed using a fiberoptic optically integrated Michelson interferometer with short coherence length superluminescent diode.

MF-ERG: Was recorded using Roland Consult (Roland Consult Electrophysiological Diagnostic System, Brandenburg, Germany) using ISCEV standard [9].

Statistical analysis

Data were fed to the computer and analyzed using SPSS software package version 20.0. One Way ANOVA test and Paired t test were used to compare between variables. Pearson correlation was used to correlate between them. The results were considered significant when the probability of error is less than 5% ($p < 0.05$).

Results

The study included 60 patients with CMO, 42 eyes had diabetic macular oedema (22 female,20 male, aged 50 ± 10 years); 12 eyes had CMO due to RVO (6 female, 6 male, the age was 49 ± 8 years) and 6 pseudophakic CMO(4 female,2 male, age was 51 ± 11 years).

In diabetic CMO

The mean log MAR of BCVA was 1.06 ± 0.24 before injection and at three months after injection, it was 0.86 ± 0.304 (p value was= 0.007). The mean intraocular pressure was 14.14 ± 1.96 mmHg before injection and at three months it was 16.14 ± 1.24 mmHg (p value was < 0.001).

Two patients (4.7%) had increased intraocular pressure and received IOP lowering eye drops but no cataract or endophthalmitis were recorded in this group.

Before injection, the mean CMT was 534.38 ± 71.23 µm and at three months after injection it significantly improved to 405.67 ± 142.48 µm (p value was < 0.001). There was marked improvement in CMT till the second month after injection. Reinjection was performed in 4 patients (9.5%) after three months from injection due to marked increase in CMT (CMT > 300 µm) (Table 1 and figure 1).

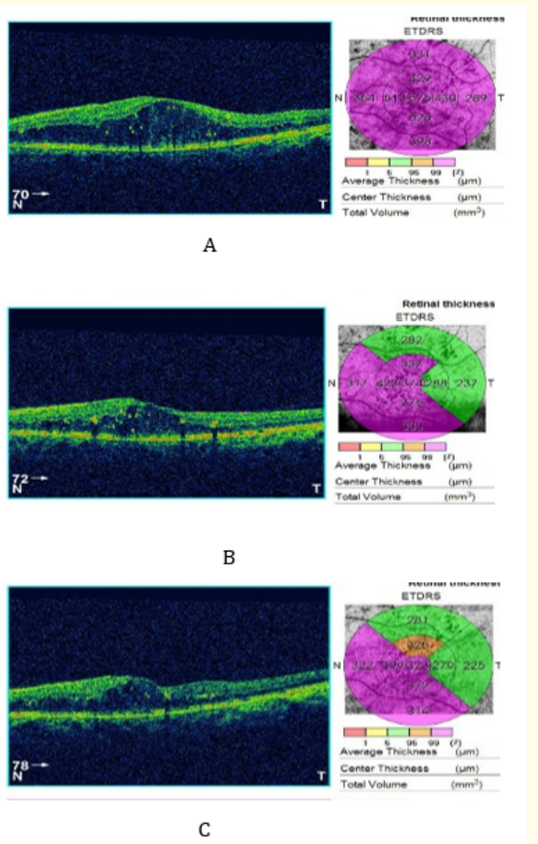

Figure 1: *Optical coherence tomography in diabetic macular edema before and after injection of trimacinolone acetate. There was reduction in macular edema after injection. A- Before injection, B- 1 month after injection, C- 3 month after injection.*

Before injection	One month after	2 months after	3 months after
534.38 ± 71.23 µm	417.62 ± 117.2 µm	399.1 ± 119.1 µm	405.67 ± 142.48 µm
	t = 6.27	t = 8.07	t = 5.304
	p < 0.001*	p < 0.001*	p < 0.001*
		t1=0.79	t1 = 0.39
		p1=0.44	p1 = 0.698
			t2 = 0.338
			p2 = 0.74

Table 1*: Central macular thickness among diabetic patients with CME before and after injection of triamcinolone acetonide.*

*t: paired t test. * p value significant < 0.05. P: Significant difference at 1,2 and 3 months after injection compared to before injection value. P1: Significant difference compared to one month after injection. P2: Significant difference compared to two months after injection.*

The mean ERG amplitude was 22.27 ± 10.48 nv before injection and at three months it was 25.28 ± 12.07 nv. The mean ERG latency was 54.32 ± 5.04 ms before injection and at three months it was 53.12 ± 6.75 ms (p value was more significant 1 and 2 months after injection (Table 2 and figure 2).

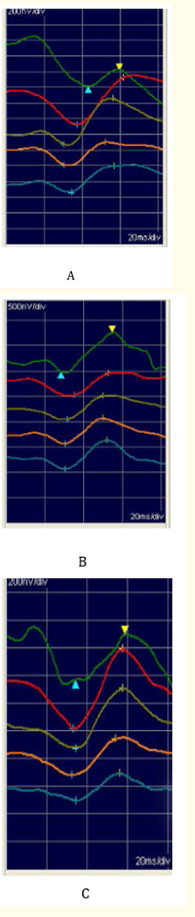

Figure 2: *MFERG (ring form) before and after injection. There were increase in the amplitude after injection. A- Before injection, B- 1 month after injection, C- 3 month after injection.*

	Before injection	One month after	2 months after	3 months after
ERG latency(ms)	54.32 ± 5.04	52.11 ± 4.83	50.98 ± 6.99	53.12 ± 6.75
		t = 2.22 p = 0.038*	t = 2.26 p = 0.035* t1 = 0.74 p1 = 0.47	t = 0.854 p = 0.403 t1 = 0.65 p1 = 0.53 t2 = 3.89 p2 = 0.001*
ERG Amplitude (nv)	22.27 ± 10.48	25.07 ± 10.21	28.75 ± 12.4	25.28 ± 12.07
		t = 2.36 p = 0.029*	t = 3.51 p = 0.002* t1 = 3.28 p1 = 0.004*	t = 1.61 p = 0.124 t1 = 0.162 p1 = 0.87 t2 = 2.48 p2 = 0.02*

Table 2: *ERG changes among diabetic patients with CME before and after injection of triamcinolone acetonide.*

In CMO with BRVO

The mean log MAR was 0.967 ± 0.34 before injection and at three months after injection it was 0.78 ± 0.18 (p value was= 0.32). The mean intraocular pressure was 15.73 ± 1.19 mmHg before injection and at three months it was 16.5 ± 0.1mmHg (p value was= 0.175). Improvement of visual acuity was marked at the second month after injection. Only one patient received IOP lowering eye drops.

Before injection CMT was 640.0 ± 56.54 µm and at three months after injection it improved to 342.67 ± 171.92 µm (p value was = 0.012) There was marked improvement in CMT at three months after IVTA (p value was = 0.012) (Table 3 and figure 3).

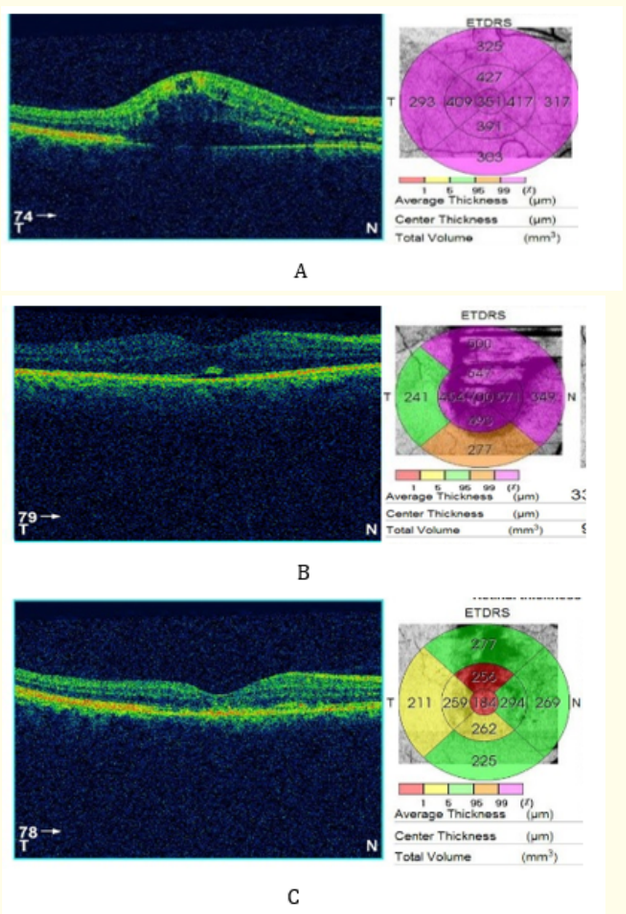

Figure 3: *Optical coherence tomography of macular edema due to center vein occulsion before and after injection of trimacinolone acetate .There was reduction in macular edema after injection. A- Before injection, B- 1 month after injection, C- 3 month after injection.*

Before injection	One month after	2 months after	3 months after
640.0 ± 56.54 µm	355.67 ± 133.91 µm	246.67 ± 33.86 µm	342.67 ± 171.92 µm
	t = 6.36	t = 10.78	t = 3.89
	p = 0.001*	p<0.001*	p = 0.012*
		t1 = 1.79	t1 = 0.108
		p1 = 0.132	p1 = 0.92
			t2 = 1.297
			p2 = 0.251

Table 3: *CMT among patients with Vein Occlusion associated with CME before and after injection of triamcinolone acetonide.*

The mean value of ERG amplitude was 28.63 ± 10.83 nv before injection and at three months it was 48.67 ± 17.37 nv. The mean value of ERG latency was 54.87 ± 4.65 ms before injection and at three months it was 53.0 ± 4.65 ms (p value was more significant at 1and2 months after injection). There was marked improvement of amplitude and decrease in latency of MF-ERG after IVTA (Table 4 and figure 4).

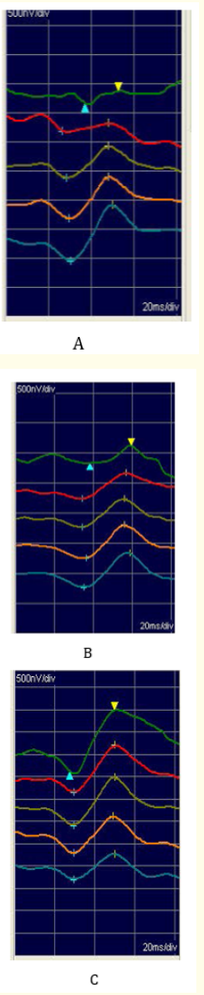

Figure 4: *MFERG (ring form) of macular edema due to CVO before and after injection . There were increase in the amplitude after injection. A- Before injection, B- 1 month after injection, C- 3 month after injection.*

	Before injection	One month after	2 months after	3 months after
ERG Latency (ms)	54.87 ± 4.65	48.67 ± 5.47	49.0 ± 0.89	53.0 ± 4.65
		t = 12.95 p<0.001*	t = 2.78 p = 0.039* t1 = 0.134 p1 = 0.899	t = 1.82 p = 0.128 t1 = 3.38 p1 = 0.02* t2 = 3.16 p2 = 0.025*
ERG amplitude (nv)	28.63 ± 10.83	37.0 ± 6.75	51.67 ± 2.73	48.67 ± 17.37
		t = 4.59 p = 0.006*	t = 5.93 p = 0.002* t1 = 7.064 p1 = 0.001*	t = 1.86 p = 0.122 t1 = 1.3 p1 = 0.25 t2 = 0.43 p2 = 0.69

Table 4: *ERG changes among patients with BRVO associated with CME before and after injection of triamcinolone acetonide.*

In pseudophakic CMO

The mean log MAR was 1.23 ± 0.21 before injection and at three months after injection it was 0.867 ± 0.23 (p value was= 0.008). The mean intraocular pressure was 14.97 ± 1.96 mmHg before injection and at three months it was 16.5 ± 0 mmHg (p value was= 0.184).

There was marked improvement in VA among pseudophakic CME. One patient received IOP lowering eye drops.

Before injection the mean CMT in pseudophakic patients with CME was 439.0 ± 170.01 µm and at three months after injection it improved to 282 ± 59 µm (Table 5 and figure 5).

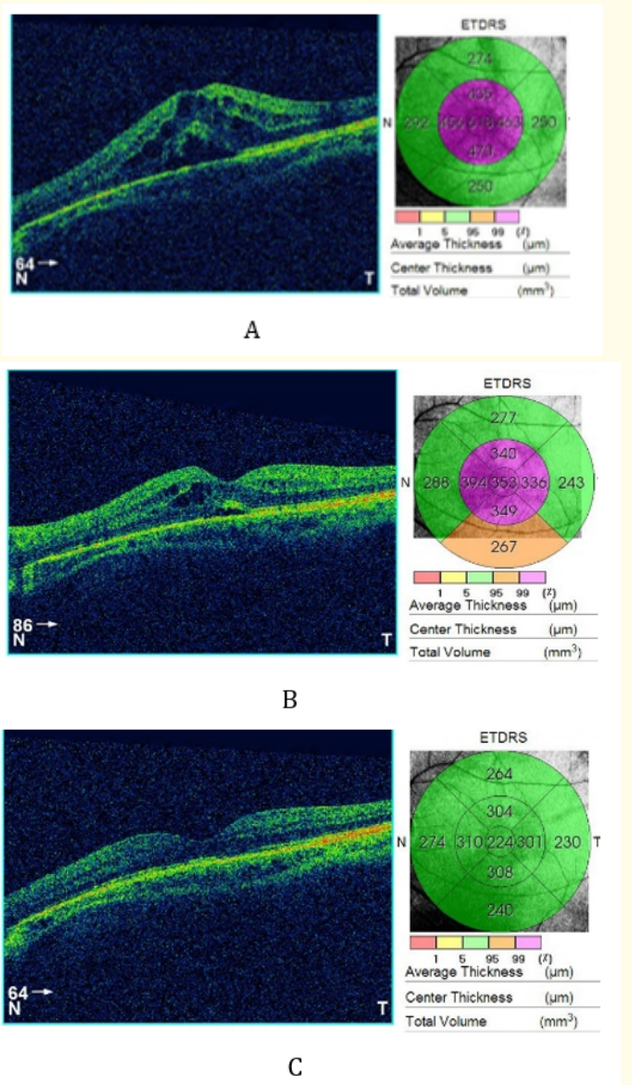

Figure 5: *Optical coherence tomography of pseuophakic macular edema before and after injection of trimacinolone acetate .There was reduction in macular edema after injection. A- Before injection, B- 1 month after injection, C- 3 month after injection.*

Before injection	One month after	2 months after	3 months after
439.0 ± 170.01 µm	255.0 ± 83.91 µm	273.0 ± 84.79 µm	282.67 ± 59.54 µm
	t = 1.82 p = 0.21	t = 3.13 p = 0.09 t1 = 0.355 p1 = 0.76	t = 1.22 p = 0.35 t1 = 0.57 p1 = 0.62 t2 = 0.127 p2 = 0.91

Table 5: *Central macular thickness among pseudophakic patients with CME before and after injection of triamcinolone acetonide.*

There was marked improvement in CMT especially at two months after injection. Reinjection was performed in 1 patient after three months from injection.

The mean ERG amplitude was 19.57 ± 4.03 nv before injection and at three months it was 26.17 ± 6.83 nv (p value was more significant at 2 months after injection (p value = 0.032). The mean ERG latency was 57.13 ± 3.07 ms before injection and at three months it was 54.0 ± 2.65 ms (p value = 0.02) (Table 6 and figure 6).

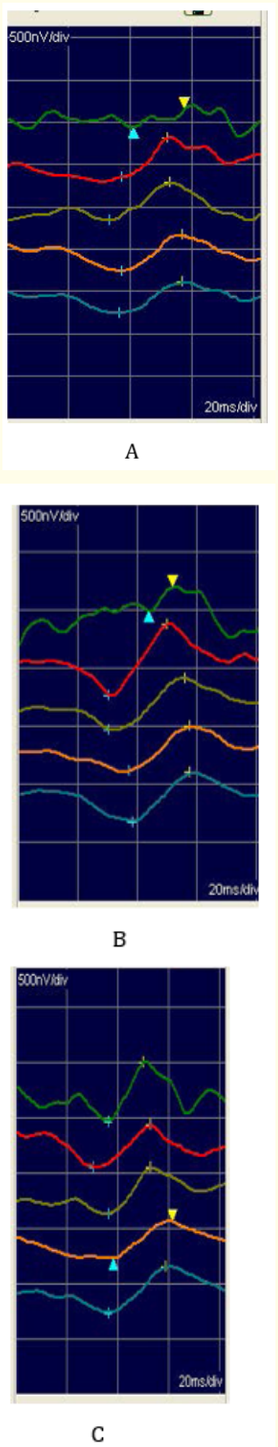

Figure 6: *MFERG (ring form) of Pseudophakic macular edema before and after injection . There were increase in the amplitude after injection. A- Before injection, B- 1 month after injection, C- 3 month after injection.*

	Before injection	One month after	2 months after	3 months after
ERG Latency (ms)	57.13 ± 3.07	55.17 ± 3.25	53.0 ± 3.07	54.0 ± 2.65
		t = 1.13 p = 0.37	t = 3.05 p = 0.093 t1 = 3.61 p1 = 0.07	t = 6.98 p = 0.02* t1 = 0.896 p1 = 0.465 t2 = 1.0 p2 = 0.423
ERG amplitude (nv)	19.57 ± 4.03	21.57 ± 1.46	29.9 ± 6.85	26.17 ± 6.83
		t = 1.19 p = 0.36	t = 5.4 p = 0.032* t1 = 2.39 p1 = 0.004*	t = 3.04 p = 0.093 t1 = 1.28 p1 = 0.33 t2 = 5.87 p2 = 0.028*

Table 6: *ERG changes among pseudophakic patients with CME before and after injection of triamcinolone acetonide.*

There were increase in intraocular pressure in four patients of 60 patients.

There was insignificant negative correlation between MF-ERG amplitude and CMT. Also, there was insignificant positive correlation between MF-ERG latency and CMT (R = -0.4, P = 0.9, R = 0.5, P = 0,3) respectively

There was positive correlation between MF-ERG amplitude and BCVA and between BCVA and CMT.

Discussion

Corticosteroids have been used for the treatment of CME, and intravitreal injection of triamcinolone acetonide has been reported since 2001 as treatment of CME. OCT can be used to quantitatively and qualitatively follow retinal thickness. OCT is a non-invasive approach and has quick imaging acquisition and safety profile [10].

Mf-ERG is a technique developed by Sutter and Tran (1992) [11]. MF-ERG utilizes an array of alternating flickers of hexagonal stimuli to stimulate individual retinal areas [12].

There was statistically significant improvement of best corrected visual acuity, decrease in OCT thickness and increase in MF-ERG amplitude in all groups of patients with CME. The improvement of BCVA was significant especially in pseudophakic patients.

In agreement with this study, Koutsandrea., *et al.* found significant improvement in visual acuity 3 months after intravitreal injection of triamcinolone acetonide. His study was performed on fourteen patients with persistent pseudophakic CME. Best corrected visual acuity and MF-ERG and OCT values increased in all patients after IVTA [13].

There was marked decrease in CMT in this study after IVTA and the result was statistically significant in RVO patients than others.

In agreement with that, Demir., *et al.* showed a significant response to intravitreal triamcinolone injection treatment with an increase in visual acuity and a reduction in central macular thickness [14].

There was decrease in the amplitude of the response and delays in implicit times in diabetic macular edema in this study.

Farahvash and Mohammed Zadoh reported that multifocal-ERG responses were significantly delayed and decreased in amplitude in patients with significant diabetic edema [15].

Similarly, Fortune., *et al.* (1999) reported that implicit times were increased and amplitudes were markedly reduced [16].

Improvement of MF-ERG values in this study was more significant at two months than after three months after injection as the CMT begin to increase again with affection of MF-ERG values.

In agreement with this study, Georgiadou., *et al.* found recurrent episodes of macular edema with recurrent damage to photoreceptors delaying or even preventing complete functional recovery [17].

Previous histopathological observations showed intracytoplasmic swelling of Müller cells, the outer plexiform layer, Henle's fiber layer is markedly swollen in diabetic eyes. Persistent retinal edema led to necrosis of Müller and adjacent neural cells and formation of cystoid cavities. So, duration of macular edema may affect both anatomical and functional results [18].

This study showed that there was insignificant correlation between CMT and amplitude of the MF-ERG before and after treatment of the macular edema (Table 5).

Similarly, Dale., *et al.* demonstrated that no significant correlations were present between OCT (structural test) and MF-ERG (functional test) parameters. They reported that functional tests will never be in complete agreement with anatomical test. They revealed disagreement between two tests. Mf-ERG tends to miss small local abnormalities that are detectable on OCT. OCT can appear normal in the face of clearly abnormal MF-ERG results. In some cases, functional damage may appear on MF-ERG before structural change is detected on OCT [19].

Durukan., *et al*. did not find any correlation between the amplitude of mf-ERG and foveal thickness. This may be due to the long-standing macular edema and the resulting damage to the photoreceptors or to a dysfunction of the neurosensory retina due to diabetes. They also found a correlation between foveal thickness and changes of amplitude of the MF-ERG after treatment. This means that although there is anatomical improvement of the macula, a residual functional impairment remains, which leads to decreased values of the mf-ERG [20].

Georgiadou., *et al.* suggested that the disturbance of visual function is in direct correlation with the degree of macular edema. The amount of intraretinal fluid acts as a barrier to transmission of the photic stimulus and activation of the photoreceptors. It might cause structural changes, such as a physical disturbance of the connections between cells and separation between neurons and their glial and vascular support [17,21,22].

In this study there was a significant negative correlation between the foveal thickness and the best corrected visual acuity at three months after IVTA.

Also, Blumenkranz and his colleagues found the same results in their study. They stated that there was an inverse correlation between BCVA and central macular thickness in patients with cystoid macular edema [23].

In this study, reinjection was performed in 8.3% of all patients with CME which include four diabetic patients and one patient with pseudophakic CMO. In this study, re-injection was performed when a patient lost 50% of the VA improvement obtained with the first injection and increase of the retinal thickness (CMT > 300 μm).

Demir., *et al.* reported that re-injections were performed at 3-months intervals when there was an increase in CMT > 100 ml or a vision loss of five or more letters [14].

The recurrence of CME is related to the disappearance of triamcinolone from the vitreous: a mean elimination half life of 18.6 days has been found, and it was estimated that 4 mg of triamcinolone would last in the vitreous for 3 months [24].

Elevation of intraocular pressure and the development of cataract are disadvantages of intravitreal triamcinolone injection therapy [25].

Four patients (6.4%) in this study received medical treatment for increased IOP. Decrease IOP after two months from injection and the IOP doesn't increase after injection directly due to the paracentesis performed intraoperatively.

This was in accordance with other studies such as Mandi., *et al.* showed that there was temporary increases in IOP that was easily controlled with topical medications [26].

Conclusion

IVTA improve retinal function and decrease macular thickness with few complications.

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