• Clinical Research •

Efficiency analysis by mfERG and OCT of intravitreal injection with ranibizumab on diabetic macular edema

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Abstract

● **AIM:** To analyze the clinical efficacy of intravitreal injection of ranibizumab (IVR) on diabetic macular edema (DME) with multifocal electroretinography (mfERG) and optical coherence tomography (OCT).

● **METHODS:** A total of 41 patients (41 eyes) with DME were treated with IVR. The best corrected visual acuity (BCVA), mfERG results, and OCT were analyzed to compare to the baselines at 1wk, 1, and 3mo after operation.

● **RESULTS:** The BCVA was significantly improved in all eyes at each time point (P<0.001). The macular area leakage and edema were reduced 1wk and 1mo after IVR, and the central fovea thickness (CFT) was significantly reduced compared to baseline (P<0.001). The mfERG, two-dimensional and three-dimensional images all showed that the macular fovea (1 ring) response density decreased, and the fovea and macular area spikes significantly decreased or disappeared. The amplitude density of the P1 wave was increased, and the latency of the P1 wave was shortened than preoperation (P<0.001). At 1wk and 1mo after the operation, there was a negative correlation between the amplitude density of P1 waves and CFT.

● **CONCLUSION:** OCT and mfERG fully demonstrate the importance of IVR for DME patients from the macular morphology and function, especially the significance of mfERG in this disease.

● **KEYWORDS:** diabetic macular edema; ranibizumab; multifocal electroretinogram; optical coherence tomography

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INTRODUCTION

Related research shows the incidence of diabetes increased with the development of economy. International Diabetes Federation showed that the number of diabetics around the world in 2011 reached 370 million, which is estimated to 550 million in 2030[1]. Diabetes is a kind of endocrine and metabolic disease affects all organs but most closely related to the eyes. Diabetes causes a series of ocular complications, such as cataract, temporary ametropia, extraocular muscles ophthalmoplegia, retinopathy, among which diabetic retinopathy (DR) has the largest number. Symptoms of DR consist of microaneurysm, eye bleeding, exudation, macular edema, formation of blood vessels, vitreous hemorrhage, amotio retinae and so on. Among all symptoms led by DR. Diabetic macular edema (DME) is one of the most serious causes of visual disability and blindness and affects approximately 14% of patients with diabetes[2]. Macular edema will cause invertible damage to visual function[3].

DME represents an accumulation of fluid within the central portion of the retina, which arises as a consequence of failure of the blood-retinal barrier (BRB). Diffuse edema is caused by extensive capillary leakage, whereas localized edema is caused by focal leakage from grouped Mas[4]. The liquid accumulates on retinal pigment epithelium, retinal nerve fiber layer, and even over the macular region, eventually resulting in DME.

Currently, the majority of treatments for DME target vascular endothelial growth factor (VEGF) to block its action. Based on this situation, the use of anti-VEGF drugs to treat DME has become a subject worth exploring. In the effort to control this disease, anti-VEGF has been successfully used to treat DME and proliferative diabetic retinopathy (PDR) resulting in improved visual and anatomic outcomes[5]. Ranibizumab is a drug cloned from VEGF antibody. It not only has a relatively small molecular weight, but also has specificity and affinity for all subtypes of human VEGF. After being combined with VEGF, antagonism inhibits neovascularization, reduces vascular permeability, reduces the permeability of the BRB, and promotes the absorption of retinal endothelial fluid to improve macular edema. Ranibizumab is a selective anti-VEGF drug used in this treatment. Several studies have demonstrated its safety and efficacy in the treatment of this disease[6-7].

Considering that DME mainly causes central vision loss, it is crucial to observe central vision aim to observe the effect of ranibizumab. In addition to the main method at present such as vision and visual field, multi-focus reproducible electrogram is an emerging visual electrophysiological method developed by Sutter and Tran[8] in 1992. The multifocal electroretinography (mfERG) is a noninvasive test that allows us to assess the functional status of the macula. Patients must fix their eyes on the central part of the monitor, and the macula is stimulated by a sequence of scaled hexagonal flashes of light projected onto it. The matrices most commonly used in clinical practice are 103 and 61 hexagons[9].

In the past, such studies have been based on changes in best corrected visual acuity (BCVA) and central fovea thickness (CFT), mainly in the morphological structure of the macular region, but this topic is not satisfied with previous observations from the morphological structure. In order to study the clinical effect of ranibizumab intravitreal injection (IVR) in the therapy of DME, this study combines optical coherence tomography (OCT) and mfERG to comprehensively analyze the retinal morphology and function of DME patients, and also provides new ideas for the study of IVR treatment of other cystoid macular edema (CME) patients.

SUBJECTS AND METHODS

Ethical Approval All patients were informed of the purpose of the study and the informed consent was obtained. The study was conducted in accordance with the Declaration of Helsinki.

Subjects All patients diagnosed with DR and macular edema in the Ophthalmology Department. The diagnosis meets the US "ETDRS" standard[10]. A total of 41 cases (41 eyes), including 18 males (18 eyes) and 23 females (23 eyes) from December 2016 to October 2018，The age range was 53-77y, with an average age of 63.7±7.6y. BCVA (logMAR): 0.4-1.7, average 0.80±0.24. CFT: 337.74-480.11 μm, average 408.90±100.67 μm.

Selection Criteria 1) patients with stage IV and below of DR; 2) disease in one or both eyes; 3) no severe visual impairment and refractive interstitial opacity; 4) BCVA (logMAR)≤2.0, refractive power ≤±3.00 DS or ±3.00 DC, central fixation; 5) stable control of blood glucose level, fasting blood glucose ≤8.0 mmol/L; 6) no other fundus lesions affecting the retina and choroid except DR; 7) without glaucoma and any history of internal eye surgery and trauma; 8) clinically significant macular edema[11]: increase in retinal thickening at or within 500 μm of the center of the macula; hard exudates at or within 500 μm of the center of the macula; if associated with the thickness of the surrounding retina. A zone or zones of retinal thickness 1 disc area in size at least part of which was within 1 disc diameter of the center. 9) no severe renal insufficiency and cerebral infarction, and show good willingness of cooperation.

Exclusion Criteria 1) diseases affect transparency of the cornea, such as cloud pheasants, cantharis, and pterygium growing into the cornea >2 mm *etc*; 2) intraocular pressure >21 mm Hg, or iris neovascularization, history of glaucoma patients; 3) accompanied by other fundus lesions affecting the retina or choroid, including retinal arteriovenous occlusion, uveitis, vitreous macular traction syndrome, anterior maculopathy, and other fundus lesions; 4) severe opacity of refractive media, including lens opacities, vitreous opacities, vitreous hemorrhage, and a large amount of hard osmosis or severe macular edema; 5) patients cannot be measured with an international standard log chart; 6) patients with cataracts, lasers, history of intraocular surgery and trauma, such as vitrectomy; 7) patients with severe heart, brain, blood vessel, and other systemic diseases cannot cooperate; 8) patients who are unwilling to undergo relevant examinations.

Methods All patients with DR and DME were diagnosed with slit lamp, fundus, optometry, OCT, and fundus fluorescein angiography. All patients signed the informed consent before injection. A ranibizumab by Novartis was inserted vertically about 4 mm behind the limbus of the temporalis and a 0.5 mg/0.05 mL of ranibizumab was injected. Record the BCVA, CFT[12-13], mfERG 1 ring P1 wave latency, and the amplitude density values. All of them were compared before and after treatment to evaluate the efficacy of ranibizumab in DME, and the correlation analysis between OCT and mfERG was performed.

Statistical Analysis SPSS 20.0 statistical software was used to process the data, and the measurement data was described as mean±standard deviation. The data of the four groups of each variable were compared using analysis of variance, and further comparisons between groups were performed using the LSD method. $P<0.001$ was considered statistically significant. The correlation between P1 wave amplitude density, P1 wave latency and CFT measured by OCT in the mfERG 1 ring was analyzed by Pearson correlation.

RESULTS

Comparison of BCVA The BCVA before IVR was 0.81±0.25. One week, 1, and 3mo after IVR, the BCVA was 0.42±0.18, 0.44±0.18 and 0.79±0.21, respectively. All comparison of BCVA at different time points before and after IVR in all affected eyes was statistically significant ($P<0.001$). One week and 1mo after IVR, BCVA was better than before surgery, and the difference was statistically significant ($P<0.001$). With time passing by, drug metabolism decreased to 3mo after surgery. Compared with 1wk and 1mo, the difference was statistically significant ($P<0.001$). There was no significant difference in the BCVA between 1wk and 1mo after operation and 3mo before and after operation ($P>0.001$; Table 1).

Central Foveal Thickness The CFT before IVR was 402.41±41.54 μm. One week, 1, and 3mo after IVR, the CFT

were 314.33±31.17, 305.67±33.52, and 399.83±40.98 μm. The overall comparison of CFT at different time points before and after IVR in all affected eyes was statistically significant (P<0.001). The macular area leakage and edema were reduced 1wk and 1mo after IVR, and the CFT was better than that before surgery. The difference was statistically significant (P<0.001). With the drug metabolism, macular edema recurred and the CFT value increased after 3mo after operation, which was significantly different from the 1wk and 1mo after operation (P<0.001), but not significantly different from that before operation (P>0.001; Table 2).

Multifocal Electroretinogram Results The mfERG waveform, two-dimensional and three-dimensional images all showed that the macular fovea (1 ring) response density decreased, and the fovea and macular area spikes significantly decreased or disappeared. The amplitude density and incubation period of P1 wave before treatment were: 18.66±3.05 nV/deg^2, 50.54±4.24ms. The amplitude density and latency of Pl wave are 30.09±5.53 nV/deg^2, 42.77±2.46ms, 30.32±5.93 nV/deg^2, 44.65±5.62ms, and 31.73±6.94 nV/deg^2, 44.67±6.36ms, after IVR for 1wk, 1, and 3mo. Compared with before treatment, the amplitude density of the P1 wave increased, and the difference was statistically significant (P<0.001); the latency of the P1 wave was shortened, and the difference was statistically significant (P<0.001; Tables 3 and 4).

Correlation of P1 Wave and Optical Coherence Tomography in Multifocal Electroretinogram 1 Ring The correlation coefficient of P1 wave amplitude density and CFT 1wk after operation is r=-0.702 (P=0.000). There is a negative correlation between the two; the correlation coefficient of P1 wave amplitude density and CFT 1mo after operation is r=-0.791 (P=0.000). There is a negative correlation between the two. There was no significant correlation between the other P1 wave latency and CFT (P>0.001; Figure 1).

DISCUSSION

This experiment comprehensively evaluated the efficacy by observing the changes in BCVA, CFT and mfERG before and after IVR treatment. All patients had an outpatient review 1wk, 1, and 3mo after surgery. Compared with before treatment, the BCVA, CFT, P1 wave amplitude density, and latency of all time points after ranibizumab treatment were improved. And do the corresponding analyses as follows: 1) Patients have a certain degree of BCVA improvement in 1wk and 1mo after treatment compared with before treatment. 2) The CFT of patients in one week and month after treatment is significantly lower than that before treatment. 3) The visual acuity decreased and the CFT increased 3mo after treatment. Xu *et al*[14] observed the efficacy of IVR in patients with DME and found that within 3mo after IVR, the BCVA increased and the CFT decreased faster. After 3mo, the improvement slowed, but it was still better than before treatment. The difference in results may be related to the number of injection, 4) The mfERG results of this study show that after IVR, the amplitude density of mfERG P1 wave is increased and the latency is shortened. This indicates that ranibizumab can improve retinal function and increase sensitivity in the foveal area of the

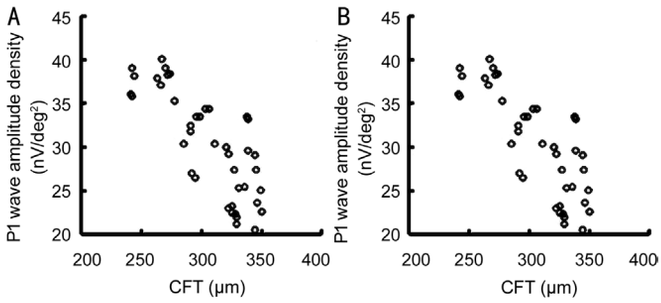

Figure 1 One-week (A) and 1mo (B) postoperative P1 wave amplitude density and CFT scatter plots.

Table 1 Comparison of BCVA

Groups	BCVA	F	P
Preop.	0.81±0.25	725.094	<0.001
Postop. 1wk	0.42±0.18[a]		
Postop. 1mo	0.44±0.18[a]		
Postop. 3mo	0.79±0.21[b,c]		

Compared with the preoperative group, [a]P<0.001; Compared with the 1wk postoperative group, [b]P<0.001; Compared with the 1mo postoperative group, [c]P<0.001.

Table 2 Comparison of CFT

Groups	CFT (μm)	F	P
Preop.	402.41±41.54	470.867	<0.001
Postop. 1wk	314.33±31.17[a]		
Postop. 1mo	305.67±33.52[a]		
Postop. 3mo	399.83±40.98[b,c]		

Compared with the preoperative group, [a]P<0.001; Compared with the 1wk postoperative group, [b]P<0.001; Compared with the 1wk postoperative group, [c]P<0.001.

Table 3 Comparison of P1 wave amplitude density nV/deg^2

Groups	P1 wave amplitude density	F	P
Preop.	18.66±3.05	146.945	<0.001
Postop. 1wk	30.09±5.53[a]		
Postop. 1mo	30.32±5.93[a]		
Postop. 3mo	31.73±6.94[a]		

Compared with the preoperative group, [a]P<0.001.

Table 4 Comparison of P1 wave latency ms

Groups	Latencies of P1 wave	F	P
Preop.	50.54±4.24	21.317	<0.001
Postop. 1wk	42.77±2.46[a]		
Postop. 1mo	44.65±5.62[a]		
Postop. 3mo	44.67±6.36[a]		

Compared with the preoperative group, [a]P<0.001.

macula. Mastropasqua *et al*[15] conducted a study on intravitreal Ozurdex® injections (IVOI) of DME patients and found that within four months after IVOI, the mfERG value did not change significantly and then began to deteriorate. This further illustrates the importance of mfERG for observing changes in retinal function after IVR treatment of DME.

Domestic research showed that the amplitude density and latency of the P1 wave were significantly different between the macular edema group and the normal control group by observing with mfERG. The change in amplitude density was related to the latency phase and more obvious than. Experts speculated that it is related to the conduction mode between nerve cells and the effect of pathological changes on cell biological characteristics. The mfERG P1 wave latency reflects changes in inner retinal function. The longer the history of DME, the more likely the photoreceptor cell layer of the retina may be affected. The more severe the damage, the longer the incubation period may appear. Persistent retinal edema is reported to result in necrosis of Müller and adjacent neural cells, leading to formation of cystoid cavities[16]. Wangsa-Wirawan and Linsenmeier's[17] study has confirmed that the P1 wave of mfERG is related to the activity of bipolar and Müller cells that dominate the middle layer of the retina.

There was a negative correlation between P1 wave amplitude density and CFT 1wk and 1mo after operation. The rest of the P1 wave latency has no significant correlation with CFT. During this follow-up, we can observe that the P1 wave amplitude density changes more significantly. This is similar to the study by Tehrani *et al*[18]. The amplitude density is more sensitive than the incubation period. So we suggest that mfERG may be a good choice in the early stage of DME patients when OCT and BCVA changes are not obvious.

The mfERG is a sensitive and objective electrophysiological detection technology, which is of great value in evaluating the function of the retina. OCT only shows structural changes in the macula, while mfERG provides information on macular function[19]. Sometimes patients with normal OCT manifestations shows damaged retinal function in mfERG. It also misses abnormal lesions found by OCT. In many cases, the damage to retinal function precedes the change in retinal morphology. Palmoski-Wolfe[20] suggests that morphological tests, such as OCT are not a substitute for functional retinal tests, such as mfERG. In summary, when studying DME, we should not only pay attention to the morphological changes of the retina, but also combine their functional changes. The mfERG is an important examination method, especially when the retinal structure has not changed significantly and the function has changed, which also provides ideas for other CME patients to perform IVR treatment. OCT is sensitive to changes in the structure of the macula, and can find the lesions missed by mfERG. The two can complement each other in clinical diagnosis and treatment and comprehensively evaluate the function and shape of the retina.

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