Original Article

Macular function assessment by multifocal electroretinogram and microperimetry in macular hole and correlation with visual acuity

Daleena Dalan[1], Durgasri Jaishankar[1], Abinaya Madhu[1], Karthiga Mani[1], Dhanashree Ratra[1]
[1]Sankara Nethralaya, 41/18, College Road, Chennai, India

Abstract

Background: Functional outcome of macular hole (MH) surgery can be better assessed with multifocal electroretinogram (mfERG) and microperimetry (MP). It might provide better assessment than the Snellen visual acuity alone.
Objectives: To evaluate macular function with mfERG and microperimetry, and assess their correlation with visual acuity in MH.
Materials and Methods: A prospective study was done in patients with unilateral, idiopathic full thickness MH. Standard surgery with vitrectomy, internal limiting membrane peeling and gas tamponade was done. Snellen and logMAR visual acuity, mfERG, microperimetry and optical coherence tomography were done pre and postoperatively.
Results: Twenty six patients with unilateral macular hole and twenty five age matched controls were included. The mean age of patients was 59.92±9.39 years (range: 40 to 74 years). All the holes were closed after surgery (two required second surgery). The mean visual acuity improved from 0.77±0.34 logMAR to 0.43±0.36 (p =0.03). The mfERG amplitudes differed ring wise, but the average amplitude changed from 26.31±8.82 to 20.52±7.11 (p =0.03). The mean retinal sensitivity changed from 12.98±2.59 to 13.42±2.53 (p =0.11). There was significant correlation between visual acuity and mfERG amplitudes and retinal sensitivity. Regression equations to predict visual outcome could be derived.
Conclusions: In MH, mfERG and microperimetry show reduced responses, delay in recovery of function. They show a strong correlation with visual acuity. It is possible to predict vision after surgery with the help of mfERG and MP. Improved ability to predict visual outcome can increase the utility of anatomic success predictors.

Key words: Internal limiting membrane peeling, Macular hole, Microperimetry, Multifocal electroretinogram, Predict visual acuity.

Financial Interest: Nil
Conflict of Interest: Nil
Received: 23.09.2019 Accepted: 20.12.2019

Corresponding author
Dr. Dhanashree Ratra, MS,DNB,FRCSEd
Department of Vitreoretinal Diseases
Medical Research Foundation, Sankara Nethralaya
41/18, College Road
Chennai, 600006, India
E-mail: dhanashreeratra@gmail.com

Introduction

Idiopathic macular hole is a major cause of central vision loss in the elderly. Vitrectomy with internal limiting membrane peeling with gas tamponade is the treatment of choice for macular hole. Despite the high anatomical closure rate of the macular hole, the functional visual improvement remains unsatisfactory. Many studies have been done to predict the visual and surgical outcomes of the macular hole surgery. Anatomic parameters such as the hole diameter, height and various indices such as the height to base diameter ratio can help predict hole closure rates (Xu et al, 2013). Preoperative laser interferometry and potential acuity meter testing can be useful in predicting vision after macular hole surgery (Smiddy et al,1994). However, they were only modestly accurate in predicting correctly the postoperative visual outcomes in macular hole patients. However, Snellen visual acuity does not accurately measure the functional outcomes of the surgery. The patient may still have difficulties like scotoma, reduced sensitivity, metamorphopsia and binocular vision disturbances (Scupola et al, 2013). Therefore, an objective evaluation of visual function can be done by assessing the retinal sensitivity and electric potential around the hole. Multifocal electroretinogram, introduced by Sutter and Tran (1992) can locate the exact point of dysfunction around the fovea from the electric potential of photoreceptors and inner retina. The recovery of function can also be recorded independent of any influences. Microperimetry is another noninvasive test to record the sensitivity of retina at various points in the central area. This study was performed to evaluate the macular function by multifocal electroretinogram (mfERG) and microperimetry (MP) before and after macular hole surgery and to correlate these with visual acuity. An attempt to predict visual acuity with the help of mfERG and MP was done.

Materials and Methods

A hospital based prospective study in which patients with idiopathic unilateral full thickness macular hole undergoing surgery were recruited from March 2016 to August 2017. Twenty six patients were recruited and 14 patients were included for follow-up. Also, 50 eyes of 25 age-matched normal controls were included for comparison. Informed consent was taken from all the persons enrolled. The study was approved by the institutional review board of our institute (Study no. 514-2016-P). The study followed the declaration of Helsinki.

Demographic details like age, sex, systemic illness were collected. All the patients underwent visual acuity, refraction, anterior segment and detailed fundus examination as a part of comprehensive eye examination. Patients with high refractive errors beyond 6 diopters, glaucoma, corneal opacities, diabetic retinopathy or any other disorder apart from macular hole were excluded. Visual acuity was recorded in logMAR and Snellen fractions, using the illuminated Snellen LED Vision Chart (ALVC-20; Appasamy Associates). Pupils were dilated with 1% tropicamide eye drops. Fundus examination was done with indirect ophthalmoscopy, and slit lamp biomicroscopy using the 78D lens. Optical coherence tomography was done using Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA) for verifying the diagnosis. Electrophysiological responses for both eyes were recorded by multifocal electroretinography system (VERIS compact, Electrodiagnostic Imaging Inc, CA, USA). It was done monocularly using the Burrian Allen contact lens electrode as active and reference electrodes and gold foil electrode as the ground electrode. The examination was done according to the guidelines of international society for clinical electrophysiology of vision (ISCEV). Amplitude and implicit time of the retinal responses in the foveal, parafoveal and perifoveal rings were measured. The size of the fixation target was increased while checking for the study eye with MH and fixation was monitored. Microperimetry was done for both the eyes monocularly using Optos scanning laser ophthalmoscope (Optos, Inc, MA,USA). The normal eyes and fellow eyes were measured first with polar 5 program using Goldman III stimulus and the eye with macular hole was assessed with a size V target. The polar 5 program tests 52 individual points arranged in 5 concentric rings in the central 21 degrees. A larger fixation target was given to the eyes with macular hole. Fixation was monitored. A 4-2-1 staircase thresholding strategy was used to map the retinal sensitivity. The mean retinal sensitivity, false positive, and false negative responses were recorded. Macular hole surgery was done with vitrectomy along with internal limiting membrane peeling and gas tamponade. The internal limiting membrane was stained with brilliant blue dye and was peeled in the standard area within the arcades. The surgery was combined with phacoemulsification and intraocular lens insertion in all phakic patients since they exhibited nuclear sclerotic changes and the patients preferred to get the combined surgery. All the tests were repeated at 1.5 months, 3 months after the surgery. Thereafter periodic follow up checks every 6 months with repeat investigations were done for some of the patients. The pre and post-surgical results of the tests were compared.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences Version 20.0 software (IBM Corp, Armonk, NY). Wilcoxon sign rank test was performed to compare the pre and post parameters. Spearman correlation was performed to find the strength and direction of association between two parameters. A p value of <0.05 was considered as significant. Linear regression was performed by the enter method to predict the change in visual acuity following surgery from the baseline mfERG and microperimetry parameters.

Results

Twenty six patients with unilateral idiopathic macular hole were included for baseline analyses and 14 patients were included for follow-up analyses. Fifty eyes of 25 age-matched normal controls were also included for comparison analyses. The mean age of patients with macular hole was 59.92±9.39 years (range: 40 to 74 years) and that of controls was 56.73 ±7.13 years (range: 40 to 70 years) (p=0.09). Out of 26 patients, the macular hole was present in the right eye for 11 (42.3%) patients and left eye for 15 (57.7%). The eye with macular hole was considered as study eye and other as fellow eye in each patient. The baseline mean visual acuity of the study eye was 0.77±0.34 logMAR and that of the fellow eye was 0.17±0.28 logMAR. After surgery, the visual acuity improved to 0.43±0.36 (p =0.03). The macular hole closed in all the 14 cases, however 2 patients required a second surgery for hole closure. None had any surgical complications. Two patients were pseudophakic to begin with, the rest 12 underwent simultaneous cataract removal. From among the 26 patients recruited in the study, 3 patients did not undergo surgery and 9 patients did not return for follow up after surgery. Hence these eyes were excluded from the follow up analysis. The follow up ranged from 3 months to 24 months. (Mean 7± 9.43 months)

The implicit time as well as the mfERG amplitudes of all rings were significantly different in patients with macular hole when compared to normal controls. The mean implicit time was 29.27±0.99 in controls and 30.05±1.31 in macular hole (p=0.009). Similarly, the mean retinal sensitivity at fovea was reduced in eyes with macular hole, but an average value for retinal sensitivity of all points showed only mild reduction from controls, which was not significant (12.98 ± 2.59 versus13.52±1.94, p =0.4).

Table 1 shows the comparison of mfERG components between normal eyes, fellow eyes and eyes with macular hole. Compared to normal, the study eyes with macular hole showed significantly delayed implicit time (except for ring 1) and reduced amplitudes in all rings. In fellow eyes, the implicit time was found to be significantly delayed in ring 5 and 6, whereas amplitude was significantly reduced in all the rings.

Table 2 shows the comparison of mfERG components at baseline and post-surgery visit at one and half months. In the study eyes, statistically significant difference was noted in the average implicit time and amplitude, ring 4 and ring 5 implicit time and amplitude, ring 6 amplitude. Worsening of both implicit time and amplitude of mfERG rings was found following surgery. The mean retinal sensitivity was seen to improve following surgery in the eyes with macular hole, but it was not statistically significant. Table 3 shows the difference in microperimetry parameters between baseline and post-surgery visit.

The correlation between logMAR visual acuity and mfERG components in the study eyes with MH, both before and after surgery was analyzed. (Table 4) The study revealed that the amplitudes of ring 2 and ring 3 and implicit time of ring 6 were significantly correlated with logMAR visual acuity. The ring 1 corresponding to the area of the macular hole, did not show any correlation with visual acuity. Whereas in the fellow eye, amplitudes of all rings except ring 5 were found to significantly correlate with logMAR visual acuity. With decreased vision, the ERG amplitude showed correspondingly reduced response density. Negative correlation was found between amplitude and logMAR visual acuity. With increasing distance away from the fovea, this correlation was not very strong. After surgery, the improvement in visual acuity was associated with reduction in mfERG amplitudes. This was reflected in the analysis and we could not detect significant correlation after surgery.

Similar to the mfERG, the retinal sensitivity on microperimetry showed a statistically significant negative correlation with logMAR visual acuity in the study eye. (Table 5) This implies that as the sensitivity decreases, the vision was found to reduce. The sensitivity of ring 3 to 5 showed significant correlation with visual acuity. Ring 1 and 2 also showed negative correlation, however were not statistically significant. In fellow eyes, the percentage of fixation within 2 degree showed significant negative correlation with baseline visual acuity. This indicates poor fixation with poorer visual acuity. But the retinal sensitivity did not show significant correlation.

In order to find prediction of change in visual acuity in macular hole eye following surgery using baseline mfERG components, linear regression was performed with enter method and the models are as follows:

Change in visual acuity (in logMAR) = 9.348 - 0.068 x Ring 1 Implicit time + 0.126 x Ring 2 Implicit time + 0.079 x Ring 3 Implicit time - 0.133 x Ring 4 Implicit time + 0.289 x Ring 5 Implicit time -0.609 x Ring 6 Implicit time

The R value of the model was 0.534 and standard error of estimate was 0.40.

Change in visual acuity (in logMAR) = -0.089 + 0.001 x Ring 1 Amplitude - 0.001 x Ring 2 Amplitude – 0.069 x Ring 3 Amplitude + 0.06 x Ring 4 Amplitude + 0.08 x Ring 5 Amplitude – 0.062 x Ring 6 Amplitude

The R value of the model was 0.717 and standard error of estimate was 0.33.

Using the baseline microperimetry sensitivity, linear regression model for visual acuity prediction was as follows:

Change in visual acuity (in logMAR) = 0.519 – 0.046 x Average sensitivity + 0.05 x Ring 1 sensitivity + 0.034 x Ring 2 sensitivity + 0.068 x Ring 3 sensitivity – 0.103 x Ring 4 sensitivity – 0.007 x Ring 5 sensitivity

The R value of the model was 0.747 and the standard error of estimate was 0.32.

Table 1: Comparison of multifocal electroretinogram (mfERG) parameters of normal eyes, fellow eyes and study eyes with macular hole

mfERG Ring		Normal (N=50)		Fellow eye (N=26)			Study eye (N=26)		
		Mean	Standard Deviation	Mean	Standard Deviation	P Value	Mean	Standard Deviation	P Value
Ring 1	Implicit time	29.95	1.52	29.77	2.64	0.252	30.61	2.7	0.543
	Amplitude	84.07	17.54	49.11	18.79	<0.0001	31.07	11.72	<0.0001
Ring 2	Implicit time	29.27	0.99	29.16	1.81	0.772	30.05	1.31	0.009
	Amplitude	60.91	9.51	36.63	14.11	<0.0001	33.59	31.63	<0.0001
Ring 3	Implicit time	29.09	1.96	29.1	1.4	0.261	29.64	1.29	0.003
	Amplitude	44.64	10.05	30.16	10.17	<0.0001	25.23	7.69	<0.0001
Ring 4	Implicit time	28.73	0.66	28.94	1.48	0.065	30.04	2.48	<0.0001
	Amplitude	35.43	9.74	25.66	8.94	<0.0001	23.13	8.15	<0.0001
Ring 5	Implicit time	28.34	3.76	29.14	0.94	0.024	29.43	0.9	0.001
	Amplitude	33.2	7.27	23.7	8.55	<0.0001	22.1	7.53	<0.0001
Ring 6	Implicit time	29.12	0.84	29.51	0.88	0.008	29.5	0.5	0.006
	Amplitude	32.8	7.39	23.13	8.52	<0.0001	22.75	8.06	<0.0001

Table 2: Pre and post-surgery comparison of multifocal electroretinogram (mfERG) components in eyes with macular hole

mfERG Ring		Study Eye				
		Pre		Post		
		Mean	SD	Mean	SD	P value
Average	Implicit time	29.88	1.25	30.76	1.92	0.030
	Amplitude	26.31	8.82	20.52	7.11	0.033
Ring 1	Implicit time	30.61	2.70	32.47	3.62	0.310
	Amplitude	31.07	11.72	29.74	14.71	0.803
Ring 2	Implicit time	30.05	1.31	31.03	2.18	0.078
	Amplitude	33.59	24.28	23.02	7.68	0.055
Ring 3	Implicit time	29.64	1.29	30.52	1.98	0.086
	Amplitude	25.23	7.69	20.41	6.22	0.021
Ring 4	Implicit time	30.04	2.48	30.43	1.56	0.003
	Amplitude	23.13	8.15	18.34	6.31	0.018
Ring 5	Implicit time	29.43	0.90	30.53	1.35	0.001
	Amplitude	22.10	7.53	16.73	6.44	0.008
Ring 6	Implicit time	39.65	0.71	30.87	1.32	0.362
	Amplitude	22.75	8.06	15.69	6.59	0.004

Pre=pre-surgery, post=post-surgery, SD=standard deviation

Table 3: Pre and post-surgery comparison of microperimetry components in the study eyes with macular hole

	Study Eye				
Components	Pre-surgery		Post-surgery		
	Mean	SD	Mean	SD	P value
Average Sensitivity	12.98	2.59	13.42	2.53	0.108
False Positive	1.00	1.75	0.42	0.90	0.655
False Negative	3.05	1.79	1.92	1.44	1.000
% within 2 degree fixation	62.32	33.18	67.50	27.49	0.528
% within 4 degree fixation	90.13	14.78	94.20	5.45	1.000

SD=standard deviation

Table 4: Correlation between visual acuity in logMAR and multifocal electroretinogram (mfERG) components before and after surgery in eyes with macular hole and in the fellow eyes.

		Study Eye Pre surgery		Study Eye Post surgery		Fellow Eye	
mfERG Ring		R value	P value	R value	P value	R value	P value
Average	Implicit time	-0.08	0.688	0.458	0.115	0.09	0.654
	Amplitude	-0.29	0.151	0.112	0.716	-0.54	0.005
Ring 1	Implicit time	0.13	0.522	0.143	0.642	0.05	0.808
	Amplitude	-0.34	0.090	0.14	0.647	-0.57	0.002
Ring 2	Implicit time	-0.20	0.323	0.4	0.175	-0.01	0.979
	Amplitude	-0.38	0.050	-0.097	0.752	-0.52	0.006
Ring 3	Implicit time	-0.19	0.345	0.293	0.331	0.11	0.598
	Amplitude	-0.49	0.012	-0.193	0.527	-0.53	0.005
Ring 4	Implicit time	-0.14	0.485	0.481	0.096	0.14	0.509
	Amplitude	-0.23	0.256	-0.068	0.824	-0.43	0.028

Table 5: Correlation between visual acuity in logMAR and microperimetry components before and after surgery in eyes with macular hole and in the fellow eyes

	Study Eye Pre Surgery		Study Eye Post Surgery		Fellow Eye	
Components	R value	P value	R value	P value	R value	P value
Average Sensitivity	-0.46	0.03	-0.682	0.01	-0.23	0.30
False Positive	0.03	0.89	0.03	0.89	-0.09	0.68
False Negative	0.30	0.18	0.218	0.474	0.34	0.13
% within 2 degree fixation	-0.06	0.80	0.127	0.679	-0.55	0.01
% within 4 degree fixation	-0.10	0.63	0.328	0.354	-0.34	0.11

Discussion

Electroretinography has been used to predict the risk of developing secondary glaucoma in central retinal vein occlusion based on the cone implicit times (Larsson et al, 1998) and the development of diabetic retinopathy in type 2 diabetes (Tyrberg et al, 2011). This study found that it can be used for visual acuity prediction after macular hole surgery also. There was a positive correlation between retinal response density with multifocal electroretinogram and visual acuity. A similar positive correlation was also seen between retinal sensitivity on microperimetry and visual acuity. The correlation was strong in the preoperative period than in the postoperative period. Predictably, the correlation was stronger for rings 2,3 and 4. Ring 1 corresponding to the macular hole understandably did not show significant results. Also, with increasing distance away from the fovea, the correlation again was poor. Post-operatively, there was reduction in the retinal response densities with multifocal ERG which can be due to multiple factors. There was significant improvement in visual acuity after macular hole surgery.

Previous authors have reported varied results about the role of mfERG in macular hole. A positive correlation was seen between the postoperative visual acuity and mfERG amplitudes, however, the amplitudes tended to vary greatly even in patients with the same level of acuity (Si et al, 1999; Moschos et al, 2001). Conversely, improvement in ERG amplitudes were noted even with unchanged visual acuities after macular hole closure (Si et al, 1999). Terasaki et al (2001) employed the use of focal macular electroretinograms for predicting postoperative visual acuity in patients with a macular hole. They noted that qualitative changes were more important than quantitative changes in ERGs for predicting postoperative visual acuity. Tilanus and associates (1999) used pattern ERG and pattern visual evoked potentials preoperatively as prognostic tools for predicting postoperative visual acuity. They found the implicit time parameters of the response to be of some prognostic value. The P100 implicit time of the 10’ check size and the pattern electroretinogram N35 implicit time were significantly associated with visual outcome (P=0.022 and P=0.042 respectively). However, the amplitudes varied based on the check size used and thus showed limited predictive value. In this study, the amplitudes of the rings 2 and 3 were significantly correlated to the vision and can be used for visual acuity prediction.

This correlation was found to become weaker in the postsurgical period. There are several reasons for this. There is a shift in the parafoveal tissue which after macular hole closure becomes foveal in position. However, this would not lead to a corresponding increase in the sensitivity of the tissue. Thus, the shift in the area may be responsible for a change in the retinal response densities. The intraretinal neural network may take as long as a year to be restored following the closure of MH (Si et al, 1999). The surgical factors such as the dye used for ILM staining and the removal of ILM itself may have an effect on the ERG responses. Many authors have documented dye toxicity leading to changes in the retinal pigment epithelial cells and photoreceptors (Sippy et al, 2001; Haritoglou et al, 2002; Enaida et al, 2006a; Enaida et al, 2006b; Kawahara et al 2007; Awad et al 2011; Nareshkumar et al, 2019). Brilliant blue dye was used in this study. A study was done to assess the effect of this dye on cultured adult retinal pigment epithelial cells which showed that it leads to cellular stress and apoptosis with increased concentration of the dye and time of contact (Nareshkumar et al, 2019). Terasaki et al (2001) found that the internal limiting membrane removal had no adverse effects on visual acuity, but there was a delay of recovery of the mfERG b-wave at 6 months after surgery.

The photopic negative response is a negative component of the photopic electroretinogram that is observed after the b-wave and is thought to originate mainly from the activity of ganglion cells and their axons. In a study by Ueno and associates (2006), it was observed that even though the macular holes were closed and visual acuities were improved without any serious complications, the amplitude of the photopic negative response was significantly reduced after surgery ($p< 0.05$), whereas the amplitude of the photopic a- and b-waves were not significantly altered. These results suggest that despite a successful macular hole surgery with no reduction in the subjective visual tests, some functional impairment in the inner retina can exist.

No improvement was seen in the retinal responses on mfERG or on microperimetry even after successful macular hole closure. However, the patients were tested soon after the surgery that is within 1 and half months. Further testing done at 3 months did show improvement in responses but this data was not included for analysis as the number of patients with all data available at 3 months was very small. A further follow up after 6 months to 1 year might reveal different results. Apostolopoulos et al (2002) also failed to note improvement at 1 month and the mfERG showed improvement only after 3 months. However, they found that the mfERG values were not correlated to best corrected visual acuity and optical coherence tomography findings at 1 year post-surgery. Studies have shown that the recovery of function of the central cones is very slow. Even after recovery of the anatomic integrity of the macula and improvement in Snellen visual acuity, the mfERG showed delayed implicit times and reduced amplitudes (; Si et al, 1999; Terasaki et al, 2001; Szlyk et al, 2005; Scupola et al, 2013). Dysfunction was seen to persist for nearly 18 months after surgery (Andréasson and Ghosh, 2014).

Contrary to the findings of the current study, Si et al (1999) found significant positive correlation of mfERG with visual acuity months after macular hole surgery. These investigators found that the retinal response densities improved, even in eyes with unchanged visual acuities. Also, in eyes with the same visual acuity, the retinal response densities in area 1 varied in a wide range. They also found that the visual acuity increased gradually until 1 year postoperatively. They concluded that a relationship does exist between the postoperative retinal response density and the visual acuity. However, the response density can vary despite the same level of visual acuity. These findings are similar to the findings of Moschos and associates (2001). Even the implicit time has been seen to correlate with visual acuity. In a study by Andréasson and Ghosh (2014), the prolonged cone 30-Hz flicker implicit time in the full-field ERG before surgery was significantly correlated to the visual acuity 6 months postoperatively ($p=0.03$). The authors postulated that the age-related structural changes in the macula such as a macular hole could be a sign of a widespread retinal disorder and the pathological and functional alterations may extend beyond the central retina.

There was significant correlation between microperimetric retinal sensitivity in the parafoveal area with visual acuity both before ($r=0.46$, $p=0.03$) and after macular hole surgery ($r= 0.68$, $p=0.01$). Amari et al (2001) found that the retinal sensitivities around the hole were unevenly distributed. They found small areas of good retinal sensitivity around the hole. The preoperative maximum parahole sensitivity correlated significantly with visual outcome. But the duration of symptoms, preoperative visual acuity, size of the macular hole, and the minimum sensitivity around the hole were not significantly correlated with visual outcome. They concluded that postoperative visual acuity can be effectively predicted by scanning laser ophthalmoscope microperimetry in macular holes. In another study, the postoperative retinal sensitivity was correlated with the size of the preoperative defect in the photoreceptor layer on optical coherence tomography (Chen et al, 2012).

The limitations of this study include a small sample size, a relatively short follow up and non-availability of serial mfERG and microperimetry data. Therefore further studies are recommended with long term follow up and repeat examinations at periodic intervals. Nevertheless, the study showed that retinal responses on mfERG and retinal sensitivity as seen on microperimetry can be used to assess macular function and even predict visual acuity after macular hole surgery.

Conclusions

The retinal sensitivity and visual acuity showed recovery after macular hole closure, however, the mfERG failed to show similar recovery. This can be attributed to inner retinal damage due to the surgical manipulations, toxicity of the dye used for staining and delay in bridging of the neural tissue. However, the mfERG amplitude and mean retinal sensitivity on microperimetry showed strong correlation with visual acuity. Visual acuity can be predicted based on mfERG and MP. This might help in further increasing the accuracy of predictions based on anatomic parameters.

References

Amari F, Ohta K, Kojima H, and Yoshimura N (2001). Predicting visual outcome after macular hole surgery using scanning laser ophthalmoscope microperimetry. Br J Ophthalmol;85:96-8.

Andréasson S, Ghosh F (2014). Cone implicit time as a predictor of visual outcome in macular hole surgery. Graefes Arch Clin Exp Ophthalmol;252:1903-9.

Apostolopoulos MN, Koutsandrea CN, Moschos MN, Alonistiotis DA, Papaspyrou AE, Mallias JA, Kyriaki TE, Theodossiadis PG, Theodossiadis GP (2002). Evaluation of successful macular hole surgery by optical coherence tomography and multifocal electroretinography. Am J Ophthalmol;134(5):667-74.

Awad D, Schrader I, Bartok M, Mohr A, Gabel D (2011). Comparative toxicology of trypan blue, brilliant blue G, and their combination together with polyethylene glycol on human pigment epithelial cells. Invest Ophthalmol Vis Sci;52:4085-90.

Chen WC, Wang Y, and Li XX (2012). Morphologic and functional evaluation before and after successful macular hole surgery using spectral-domain optical coherence tomography combined with microperimetry. Retina;32:1733-42.

Enaida H, Hisatomi T, Goto Y, Hata Y, Ueno A, Miura M, Kubota T, Ishibashi T (2006). Preclinical investigation of internal limiting membrane staining and peeling using intravitreal brilliant blue G. Retina;26:623-30.

Enaida H, Hisatomi T, Hata Y, Ueno A, Goto Y, Yamada T, Kubota T, Ishibashi T (2006) . Brilliant blue G selectively stains the internal limiting membrane/brilliant blue G-assisted membrane peeling. Retina;26:631-6.

Haritoglou C, Gandorfer A, Gass CA, Schaumberger M, Ulbig MW, Kampik A (2002). Indocyanine green-assisted peeling of the internal limiting membrane in macular hole surgery affects visual outcome: a clinicopathologic correlation. Am J Ophthalmol;134:836-41.

Kawahara S, Hata Y, Miura M, Kita T, Sengoku A, Nakao S, Mochizuki Y, Enaida H, Ueno A, Hafezi-Moghadam A, Ishibashi T (2007). Intracellular events in retinal glial cells exposed to ICG and BBG. *Invest* Ophthalmol Vis Sci; 48:4426–32.

Larsson J, Andreasson S, Bauer B (1998). Cone b-wave implicit time as an early predictor of rubeosis in central retinal vein occlusion. Am J Ophthalmol;125:247–9.

Moschos M, Apostolopoulos M, Ladas J, Theodossiadis P, Malias J, Moschou M, Papaspirou A, Theodossiadis G (2001). Multifocal ERG changes before and after macular hole surgery. Doc Ophthalmol;102:31-40.

Nareshkumar RN, Karthikkeyan G, Ratra D, Coral K (2019). Effect of brilliant Blue-G on cellular stress response in retinal pigment epithelial cells: In vitro. Exp Eye Res;181:157-62.

Scupola A, Mastrocola A, Sasso P, Fasciani R, Montrone L, Falsini B, Abed E (2013). Assessment of retinal function before and after idiopathic macular hole surgery. Am J Ophthalmol;156:132-139.

Si YJ, Kishi S, and Aoyagi K (1999). Assessment of macular function by multifocal electroretinogram before and after macular hole surgery. Br J Ophthalmol.;83:420-4.

Sippy BD, Engelbrecht NE, Hubbard GB, Moriarty SE, Jiang S, Aaberg TM Jr, Aaberg TM Sr, Grossniklaus HE, Sternberg P Jr (2001). Indocyanine green effect on cultured human retinal pigment epithelial cells: implication for macular hole surgery. Am J Ophthalmol;132:433-5.

Smiddy WE, Thomley ML, Knighton RW, Feuer WJ (1994). Use of the potential acuity meter and laser interferometer to predict visual acuity after macular hole surgery. Retina;14: 305–9.

Sutter EE, Tran D (1992). The field topography of ERG components in man--I. The photopic luminance response. Vision Res;32:433-46.

Szlyk JP, Vajaranant TS, Rana R, Lai WW, Pulido JS, Paliga J, Blair NP, Seiple W (2005). Assessing responses of the macula in patients with macular holes using a new system measuring localized visual acuity and the mfERG. Doc Ophthalmol;110:181-91.

Terasaki H, Miyake Y, Nomura R, Piao CH, Hori K, Niwa T, Kondo M (2001). Focal macular ERGs in eyes after removal of macular ILM during macular hole surgery. Invest Ophthalmol Vis Sci;42:229-34.

Tilanus MA, Cuypers MH, Bemelmans NA, Pinckers AJ, Deutman AF (1999). Predictive value of pattern VEP, pattern ERG and hole size in macular hole surgery. Graefes Arch Clin Exp Ophthalmol;237:629-35.

Tyrberg M, Lindblad U, Melander A, Lövestam-Adrian M, Ponjavic V, Andréasson S (2011). Electrophysiological studies in newly onset type 2 diabetes without visible vascular retinopathy. Doc Ophthalmol;123:193–8.

Ueno S, Kondo M, Piao CH, Ikenoya K, Miyake Y, Terasaki H (2006).Selective amplitude reduction of the PhNR after macular hole surgery: ganglion cell damage related to ICG-assisted ILM peeling and gas tamponade. Invest Ophthalmol Vis Sci;47:3545–9.

Xu D, Yuan A, Kaiser PK, Srivastava SK, Singh RP, Sears JE, Martin DF, Ehlers JP (2013). A novel segmentation algorithm for volumetric analysis of macular hole boundaries identified with optical coherence tomography. Invest Ophthalmol Vis Sci;54:163-9.