Effect of vitrectomy for epiretinal membrane on visual function and vision-related quality of life

Fumiki Okamoto, MD, Yoshifumi Okamoto, MD, Takahiro Hiraoka, MD, Tetsuro Oshika, MD.

Department of Ophthalmology, Institute of Clinical Medicine, University of Tsukuba, Ibaraki, Japan

Short title: Vision-related QOL in ERM

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Correspondence to Fumiki Okamoto, MD, Department of Ophthalmology, Institute of Clinical Medicine, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba, Ibaraki, 305-8575 Japan. E-mail: Fumiki-o@md.tsukuba.ac.jp FAX: +81-29-853-3148
Epiretinal membrane (ERM) is a non-vascular fibrocellular proliferation that develops on the surface of the internal limiting membrane, resulting in retinal wrinkling and distortion. The prevalence of ERM formation is 5.3% to 18.5% of the population. The first report of successful removal of ERM was published by Machemer in 1978. Since then, favorable visual outcome has been achieved in the majority of cases postoperatively. Visual acuity improves in many patients after successful removal of ERM, whereas it has been reported that metamorphopsia can still be present even if ERM was successfully removed with improvement of visual acuity. Metamorphopsia occurring in eyes with ERM is one of the most common conditions responsible for deterioration in vision-related quality of life (VR-QOL); however, relatively little attention has been paid to the relationship between metamorphopsia and VR-QOL in patients with ERM.

In ophthalmology, traditional objective clinical outcome measures such as visual acuity are increasingly being complemented with assessment of patients' perception of their visual function and quality of life. The National Eye Institute 25-Item Visual Function Questionnaire (VFQ-25) is a VR-QOL instrument designed to assess patients' perception of their visual function and QOL. The VFQ-25 has been used to track the outcome of many ocular diseases such as cataract, glaucoma, age-related macular degeneration, diabetic retinopathy, macular hole, rhegmatogenous retinal detachment, and keratoconus.

A recent study using VFQ-25 demonstrated that vitrectomy for ERM had a beneficial effect on patients' subjective perception of visual function, and the VFQ-25 responses correlated with visual acuity, but not with contrast sensitivity and metamorphopsia in patients with ERM. This study used the Amsler charts, which have been widely used to detect and evaluate metamorphopsia in patients with macular diseases. With the Amsler charges, however, it is difficult to quantify the severity of metamorphopsia because the patients have to self describe the degree of image distortion. An M-CHARTS (Inami Co., Tokyo, Japan) is an instrument which can easily and quantitatively evaluate the degree of metamorphopsia associated with macular diseases, with the patients only to answer whether the line is distorted or not. The purpose of this study was to evaluate VR-QOL in patients with ERM, and to investigate the relationship between VR-QOL and visual function including metamorphopsia.

Methods

Patients

We included 28 eyes of 28 consecutive patients with ERM who were undergoing pars plana vitrectomy at Tsukuba University Hospital between July 28, 2005, and February 20, 2007. There were 13 males and 15 females, and their age averaged 66.7 ± 8.5 years (mean ± SD). Twenty-six age-matched subjects served as normal controls (12 males and 14 females, age 64.1 ± 10.4 years). This study was conducted in accordance with the tenets of the Declaration of Helsinki, and the study protocol was approved by the institutional review committees. Prior to inclusion in the study, the nature of the study was explained to all patients, and their written informed consent was obtained. ERM was defined as a translucent or semi-translucent membrane with macular thickening involving
the center of the macula, with or without distortion and wrinkling of the inner retinal surface on biomicroscopy and optical coherence tomography (OCT). Exclusion criteria included patients with a previous history of vitreoretinal surgery and ophthalmic disorders, except for mild refractive errors and mild cataract. Eyes with secondary ERM due to retinal vascular disease, uveitis, trauma, and retinal breaks were also excluded from the study.

Data were collected for logMAR best-corrected visual acuity (BCVA), letter contrast sensitivity, and metamorphopsia preoperatively and at 3 months postoperatively. Letter contrast sensitivity was measured using the CSV-1000LV chart (Vector Vision, Columbus, Ohio).

The severity of metamorphopsia was evaluated by the M-Charts. M-Charts consist of 19 dotted lines with dot intervals ranging from 0.2 degrees to 2.0 degrees of visual angle. If the straight line is substituted with a dotted line and the dot interval is changed from fine to coarse, the distortion of the line decreases with the increasing dot interval, until the dotted line appears straight. At first, vertical straight lines (0 degrees) were shown to the patient. If the patient recognized the straight line as straight, the metamorphopsia score was 0. If the patient recognized the straight line as irregular or curved, then subsequent pages of M-Charts, in which the dot intervals of the dotted line change from fine to coarse, were shown one after another. When the patient recognized a dotted line as being straight, the visual angle that separated the dots was considered to represent his/her metamorphopsia score for vertical line. Also, the M-Charts were rotated 90 degrees and the same test is performed using horizontal lines. The examinations were repeated three times for each subject to evaluated the reproducibility of the test, and their mean was used for data analyses. The examination was performed at 30 cm and the refraction of the eye was exactly corrected for this distance.

Central macular thickness was measured using OCT (Stratus OCT 3000, Carl Zeiss Ophthalmic Systems-Humphrey Division, Dublin, CA, USA) preoperatively and at 3 months postoperatively. OCT was performed with the fast macular thickness map mode, and central macular thickness was obtained from the retinal map analysis function.

**Surgical procedures**

All surgeries were performed by a single surgeon (F.O.) under sub-Tenon local anesthesia. The lens was removed by phacoemulsification and intraocular lens implantation when required, following which vitrectomy was performed. The surgical technique used was standard 20-gauge three-port pars plana vitrectomy. With conventional contact lenses, posterior hyaloid separation and removal of the posterior vitreous membrane were performed. The ERM was engaged and removed from the macula with a pick and intraocular forceps. Peripheral retinal examination with scleral depression was performed to search for a retinal tear or dialysis. Air-fluid exchange was performed if iatrogenic retinal tear and/or rhegmatogenous retinal detachment were identified intraoperatively.

**VFQ-25**

The patients answered VFQ-25 preoperatively and 3 months
postoperatively. Preoperative VFQ-25 was administered 1-2 days before surgery. The research staff explained the questionnaire to the patients, verbally administered instructions, and provided assistance when required. The completed questionnaires were reviewed for missing data by the research staff. Prior to surgery, all the missing items were incorporated by the subjects themselves.

The VFQ-25 comprises 25 items wherein patients are expected to assess the level of difficulty of particular visual symptoms or day-to-day activities. Each item is assigned to one of the 12 subscales, namely, general health, general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, and peripheral vision. The subscales are scored on a 0- to 100-point scale, where 100 indicates the highest possible function or the minimal subjective impairment. The VFQ-25 composite score is calculated as the unweighted average response to all items, excluding the questions on general health. The VFQ-25 used in this study was a Japanese version, with modifications to suit the Japanese culture and lifestyle. The modified NEI VFQ-25 questionnaire has been assessed for reliability and validity, and it has been proven to accurately measure VR-QOL in Japanese individuals.

**Statistical analysis**

The mean scores and standard deviations were calculated for each VFQ-25 subscale as well as composite score, in patients with ERM and normal controls. The Mann-Whitney $U$ test was performed to compare each subscale score and composite score between ERM patients and normal controls. The Wilcoxon signed-ranks test was used to compare preoperative and postoperative results. The relationship between the questionnaire scores and visual acuity, contrast sensitivity, metamorphopsia, central macular thickness, and age were examined by the Spearman rank correlation test. All tests of association were considered statistically significant if $P < 0.05$. The analyses were carried out using StatView (version 5.0, SAS Inc., Cary, NC, USA).

**Results**

Among the 28 patients with ERM, 8 were pseudophakic and 20 were phakic. Eighteen of 20 patients who had slight or moderate lens opacity underwent combined cataract surgery and vitrectomy to avoid cataract formation following vitrectomy. No significant intraoperative and postoperative complications were observed, such as retinal detachment, choroidal detachment, subretinal hemorrhage, cataract formation, and infection. Air-fluid exchange was performed in 7 patients because of intraoperative identification of retinal tears. In 2 patients, intraocular pressure elevated above than 25 mmHg, and antihypertensive agent was administered. These patients responded to treatment, and antihypertensive agent was discontinued within 3 days.

Vitrectomy significantly improved logMAR BCVA from $0.495 \pm 0.293$ preoperatively to $0.245 \pm 0.294$ postoperatively ($P < 0.0001$). Sixteen patients (57.1%) gained 2 or more early treatment diabetic retinopathy study (ETDRS) lines. No change in logMAR BCVA was observed in 11 eyes (39.3%), and vision
decreased by 1 or more lines in 1 patient (3.6%). The postoperative reduction in visual acuity was attributed to retinal atrophy of the macula. Twenty-seven (96.4%) patients underwent ERM surgery in their worse-seeing eye. LogMAR BCVA in the fellow eye was 0.062 ± 0.191. The letter contrast sensitivity significantly increased from 14.6 ± 5.3 preoperatively to 18.6 ± 5.5 postoperatively ($P < 0.0001$). The severity of metamorphopsia also significantly improved from 0.79 ± 0.47 preoperatively to 0.33 ± 0.44 postoperatively ($P = 0.0005$). Central macular thickness also significantly improved from 440 ± 106 μm to 315 ± 89 μm ($P < 0.0001$).

The results of VFQ-25 questionnaire pre- and postoperatively are summarized in Table 1. The preoperative VFQ-25 composite score was significantly lower in the ERM patients than in the normal controls ($P < 0.0001$). The preoperative subscale scores were significantly lower in the ERM patients than in the normal controls in all subscales, except for general health and ocular pain. Membrane peeling surgery significantly improved VFQ-25 composite score ($P < 0.0001$) and the scores in 10 out of 12 subscales, except for general health and peripheral vision. However, postoperative VFQ-25 composite score still remained significantly lower in the ERM patients than in the normal controls ($P < 0.0001$).

The preoperative VFQ-25 composite score exhibited significant correlation with the severity of preoperative metamorphopsia ($r = -0.411$, $P < 0.05$, Fig 1). No correlation was observed between preoperative VFQ-25 composite score and preoperative logMAR BCVA ($r = 0.018$, $P = 0.928$), letter contrast sensitivity ($r = 0.092$, $P = 0.659$), central macular thickness ($r = 0.162$, $P = 0.415$), and age ($r = -0.010$, $P = 0.960$).

The postoperative VFQ-25 composite score exhibited significant correlation with the severity of postoperative metamorphopsia ($r = -0.393$, $P < 0.05$, Fig 2) and postoperative logMAR BCVA ($r = -0.373$, $P < 0.05$), but not with letter contrast sensitivity ($r = 0.170$, $P = 0.411$). The correlation between the postoperative VFQ-25 composite score and central macular thickness was borderline significance ($r = -0.372$, $P = 0.051$).

Changes in VFQ-25 composite score significantly correlated with changes in the severity of metamorphopsia ($r = -0.411$, $P < 0.05$, Fig 3). There was no significant correlation between changes in VFQ-25 composite score and changes in logMAR BCVA ($r = -0.076$, $P = 0.705$), letter contrast sensitivity ($r = 0.267$, $P = 0.189$), and central macular thickness ($r = 0.05$, $P = 0.804$).

LogMAR BCVA in the fellow eye did not show any significant relationship with preoperative VFQ-25 composite score ($r = 0.115$, $p = 0.563$), postoperative VFQ-25 composite score ($r = 0.156$, $p = 0.432$), and changes in VFQ-25 composite score ($r = -0.178$, $p = 0.369$).

**Discussion**

In the present study, VFQ-25 composite score and all subscale scores, except for general health and ocular pain, were significantly deteriorated in patients with ERM compared to the normal controls. Vitrectomy to remove ERM significantly improved not only visual acuity, contrast sensitivity, and central macular thickness, but also VFQ-25 scores. Previous studies have reported that
the mean VFQ-25 composite scores after vitreoretinal surgery in patients with macular hole, rhegmatogenous retinal detachment, proliferative diabetic retinopathy, and age-related macular degeneration were 82.4, 80.3, 68.5, and 54.4, respectively. The mean VFQ-25 composite score after ERM surgery in this study (77.9) was similar to those after macular hole and rhegmatogenous retinal detachment surgery and higher than those after vitrectomy for proliferative diabetic retinopathy and age-related macular degeneration.

ERM surgery significantly improved the mean VFQ-25 composite score from 66.2 preoperatively to 77.9 postoperatively. This improvement of VR-QOL in patients with ERM was higher than these in macular hole and age-related macular degeneration. Gupta OP et al. demonstrated that ERM surgery was a very cost-effective procedure using quality-adjusted-life-years (QALYs) methods. The cost-effectiveness ratio for ERM surgery was higher than that for macular hole surgery. Thus, ERM surgery improved VR-QOL and was a cost-effective intervention compared to other vitreoretinal surgeries.

As shown in the results, even after successful membrane peeling surgery in patients with ERM, VR-QOL remained at a lower level than the normal controls. This finding is consistent with the results of previous case-control studies on VR-QOL for retinal disorders such as rhegmatogenous retinal detachment and proliferative diabetic retinopathy.

In our study, VR-QOL was significantly associated with the severity of metamorphopsia before and after surgery. In addition, changes in VR-QOL were associated with changes in metamorphopsia. This observation is not consistent with the results of previous studies in patients with ERM and macular hole. Ghazi-Nouri et al. showed that VFQ-25 responses correlated with visual acuity but not with contrast sensitivity and metamorphopsia in patients with ERM. Tranos et al. investigated VR-QOL in patients with macular hole and observed that postoperative VFQ-25 responses significantly correlated with postoperative metamorphopsia, whereas preoperative and change in VFQ-25 composite score by surgery were not associated with the degree of metamorphopsia. Such discrepancy between our and previous studies may be attributable to the different methods of evaluating metamorphopsia. In previous studies, the severity of metamorphopsia was graded using the Amsler charts, which have been widely used to detect metamorphopsia in macular diseases. As the methods of evaluating metamorphopsia are numbered distorted squares on the Amsler chart, the result indicates mainly extent of central metamorphopsia. On the other hand, the M-Charts have been used to quantify severity of metamorphopsia in patients with ERM and macular hole. The M-Charts can evaluate frequency components of distortion in metamorphopsia. The fine high frequency component of metamorphopsia which is usually observed in mild ERM is detect by fine dotted lines, however, it is not detected by coarse dotted lines. In severe ERM, the large amplitude and low frequency components of metamorphopsia increase, so it is easy to detect by all kinds of lines, including coarse dotted lines. Thus, VR-QOL seems to be associated with the frequency components of distortion in metamorphopsia, but not with extent of central metamorphopsia.

The preoperative VFQ-25 composite score significantly correlated with the severity of preoperative metamorphopsia, but not with preoperative visual acuity.
In addition, changes in VFQ-25 composite score correlated with changes in metamorphopsia, but not with changes in visual acuity. Many studies have shown that visual acuity correlates with VR-QOL in patients with vitreoretinal disorders such as ERM, macular hole, proliferative diabetic retinopathy, age-related macular degeneration, and central retinal vein occlusion. The preoperative visual acuities in this study were relatively good with a mean preoperative logMAR BCVA of 0.495 and a mean postoperative logMAR BCVA of 0.295. These good preoperative visual acuities may also explain why VFQ-25 did not correlate with visual acuity since patients had not lost that much vision before they had surgery. Wong JG et al. interviewed 91 patients with ERM to assess the influence of surgery on functional vision. They reported that the frequency of patients with ERM complained of moderate to severe distortion decreased from 80% to 30% by surgery. On the other hand, the frequency of patients complained of visual disturbance decreased from 55% to 30% by surgery. Bouwens MD et al. quantitatively evaluated the severity of metamorphopsia in patients undergoing ERM using Sine Amsler Chart and observed that metamorphopsia improved in 82% patients, while visual acuity improved only in 48% by surgery. Judging from these previous and our findings, it seems that ERM peeling surgery is highly effective in improving metamorphopsia, but significant improvement of visual acuity may not be expected in many cases. In practice, surgical indication and outcome measures are judged mainly based on visual acuity parameters. Postoperatively, however, many patients complain of significant symptoms other than blurred vision, especially distortion, which is not adequately reflected by visual acuity assessment. In light of VR-QOL, we must pay more attention to the degree of and changes in metamorphopsia in patients with ERM.

Our study has several limitations. First, there may be some placebo effect for taking the VFQ-25 before and after surgery. The patients obviously know they had surgery and may have answered the VFQ-25 questions more positively following surgery due to an expectation that they would benefit from the surgery. This cannot be avoided by the study design, but could account for some of the improvements in the VFQ-25. Second, the sample size in our study was rather small, and that may have influenced the relationship between visual function and VFQ-25 scores. Third, postoperative follow-up was short. We evaluated the patients at 3 months postoperatively. A long-term follow-up study in vitrectomy for ERM reported that visual improvement was archived in 43% of eyes at 6 to 12 months, in 54% at 1 to 2 years, and 60% at 2 to 3 years. Future studies with a larger sample size and longer follow-up period will further facilitate our understanding of the relationship between VR-QOL and visual function in patients undergoing surgery for ERM.

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review of the manuscript (T.O.); and approval of the manuscript (F.O., Y.O., T.H., T.O.). This study was approved by the Institutional Review Board at the Tsukuba University Hospital and was in adherence to the tenets of the Declaration of Helsinki.
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Figure legends

Figure 1. Preoperative National Eye Institute 25-Item Visual Function Questionnaire (VFQ-25) composite score vs. severity of preoperative metamorphopsia in patients with epiretinal membrane.

Figure 2. Postoperative National Eye Institute 25-Item Visual Function Questionnaire (VFQ-25) composite score vs. severity of postoperative metamorphopsia in patients with epiretinal membrane.

Figure 3. Changes in National Eye Institute 25-Item Visual Function Questionnaire (VFQ-25) composite score vs. changes in severity of metamorphopsia after epiretinal membrane peeling surgery.