EVALUATION OF ANATOMICAL AND FUNCTIONAL OUTCOME OF EPIRETINAL MEMBRANE SURGERY IN PATIENTS WITH IDIOPATHIC EPIRETINAL MEMBRANE

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DISCLAIMER

I hereby certify that the work in this dissertation is my own except for the quotations and summaries which have been duly acknowledged. I declare that I have no financial interest in the instruments in this study.

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ABSTRAK

OBJEKTIF

Untuk menilai hasil anatomi dan fungsi membran epiretinal (ERM) idiopatik antara kumpulan pemerhatian dan kumpulan intervensi pada 6 bulan selepas pembedahan.

KAEDAH KAJIAN

Kajian kohort prospektif dilakukan terhadap semua pesakit ERM idiopatik yang memenuhi kriteria inklusi telah dipilih. Data yang direkodkan termasuk tahun diagnosis ERM, tempoh simptom, umur semasa diagnosis, jantina, etnik, dan kehadiran patologi okular lain. Ketajaman penglihatan (KP), status kanta, konfigurasi ERM, dan ketebalan min subfield pusat (SPT), integriti zon ellipsoid (ZE), dan lapisan dalam retina tidak teratur (LDRTT) dalam tomografi koheren optik domain spektrum (SD-OCT) telah direkodkan untuk semua pesakit semasa diagnosis dibuat dan 6 bulan selepas diagnosis untuk kumpulan observasi dan semasa diagnosis dan 6 buan setelah pembedahan untuk kumpulan intervensi. Pesakit menerima maklumat tentang simptom yang dikaitkan dengan ERM, pilihan rawatan dan perkembangan penyakit, kemudian membuat persetujuan termaklum mengenai pelan rawatan.

KEPUTUSAN

Enam puluh subjek (30 intervensi dan 30 pemerhatian) telah diambil untuk kajian ini. Purata umur dalam kumpulan pemerhatian dan intervensi ialah 64.10$\pm$7.4 dan 62.70$\pm$8.44 tahun, masing-masing. Purata SPT semasa diagnosis ialah 357.13$\pm$59.57 μm dan 410.03$\pm$89.06 μm masing-masing dalam kumpulan pemerhatian dan kumpulan intervensi. Perbezaan min dan selang keyakinan 95% dalam SPT selepas 6 bulan ialah -

69.67 (-99.17, -40.17) dengan perbezaan yang ketara di kalangan kumpulan dalam SPT pasca intervensi ($p<0.001$). Terdapat perkaitan yang ketara bagi integriti ZE antara kumpulan ($p<0.001$), 95% CI bagi perbezaan min: (-0.13, -0.01).

Sementara itu, tidak terdapat perkaitan yang signifikan LDRTT antara kedua-dua kumpulan ($p=0.23$), dengan perbezaan min 95% CI (-0.13, -0.01). Tambahan pula, purata KP pasca intervensi antara KP pra dan pasca intervensi adalah berbeza secara ketara ($p<0.001$), dengan perbezaan min 95% CI (-0.85, -0.28). Akhir sekali, terdapat kaitan yang signifikan antara tempoh ERM, pra pembedahan KP dan intergriti ZE dengan KP 6 bulan pasca intervensi ($b=.023$, 95% CI .001, $p<0.05$).

KESIMPULAN

Pembedahan ERM telah menunjukkan hasil yang positif pada aspek anatomi dan fungsi. Penanda bio SD-OCT, seperti SPT dan ZE mempunyai kaitan signifikan terhadap KP pasca intervensi. Jelas sekali bahawa tempoh ERM yang lebih lama mempunyai kesan minimum ke atas hasilnya.

Kata kunci: LogMar, ketajaman penglihatan, lapisan dalam retina tidak teratur, ketebalan min subfield pusat, integriti zon elipsoid, membran epiretinal

ABSTRACT

Objective: To evaluate anatomical and functional outcomes of an idiopathic epi-retinal membrane (ERM) between observation group and intervention group at 6-month post-operative.

Design: Prospective Cohort study.

Participants: Patients who met the clinical diagnosis of idiopathic ERM in the age frame of 18-80 years; patients with reduced visual acuity (VA), with best corrected VA of 0.2 LogMar or worse, with symptoms of significant metamorphopsia, who visited our center from June 2021 to June 2022.

Methods: All idiopathic ERM patients who fulfilled the inclusion criteria were selected. The data recorded included the year of ERM diagnosis, duration of symptoms, age at diagnosis, gender, ethnicity, and presence of other ocular pathologies. VA, lens status, ERM configuration, and central subfield mean thickness (CST), ellipsoid zone integrity (EZ), and disorganized retinal inner layer (DRIL) in spectral domain-optical coherence tomography (SD-OCT) were recorded for all patients at diagnosis and 6 months after diagnosis in observation group and at diagnosis and 6 months post-surgery for intervention group. Patients received information on the symptoms associated with ERM, treatment options, and disease progression, then made informed consent of the treatment plan.

Main Outcome Measures: VA, CST, EZ and DRIL at diagnosis and 6 months.

Result:

Sixty subjects (30 observation and 30 interventional arms) were recruited for this study. The mean age in the observation and interventional groups was 64.10 ± 7.4 years and 62.70 ± 8.44 years, respectively. The mean at diagnosis CST was 357.13 ± 59.57 μm and 410.03 ± 89.06 μm in the observation group and intervention group respectively. The mean difference and 95% confidence interval in post-op CST were - 69.67 (-99.17, -40.17) with significant differences among groups in post-op CST ($p<0.001$).

There was a significant association of EZ integrity between groups ($p<0.001$), 95% CI of mean difference: (-0.13, -0.01). Meanwhile, there is no significant association of DRIL between both groups ($p=0.23$), with 95% CI of mean difference (-0.13, -0.01). Furthermore, the mean VA after 6 months and VA Change between observation and intervention groups are significantly different ($p<0.001$), with 95% CI of mean difference (-0.85, -0.28) and (-0.68, -0.27) respectively. Finally, there is a significant association between the duration of ERM, preoperative VA, intact EZ and CST with post-operation VA outcome at 6 months post-intervention ($p<0.05$).

Conclusion

ERM surgery has shown positive outcomes on anatomical and functional aspects. SD-OCT biomarkers, such as CST and EZ have significant association with post-operative visual outcome. It is evident that a longer duration of ERM does have a minimal impact on the outcome.

Keywords: LogMar, visual acuity, disorganized retinal inner layer, central subfield mean thickness, ellipsoid zone integrity, epiretinal membrane.

Chapter 1
Introduction

1.1 EPIRETINAL MEMBRANE (ERM)

Epiretinal membrane or commonly called ERM is a sheet like fibrous material that develops on the surface of inner retina. This disease was identified in 1865 [1]. ERM commonly involves elderly age group and can be classified into idiopathic or secondary due to various ocular conditions [2-3]. Idiopathic ERM is when there is no causative factors or ocular pathology meanwhile secondary ERM commonly found in retinal breaks, retinal detachment, retinal vascular diseases, proliferative vitreoretinopathy, ocular inflammation, and procedures such as photocoagulation or retinal cryopexy.

In addition to etiological classification, Gass has classified ERM into 3 grades based on bio microscopical features. Grade 0 is membrane or cellophane maculopathy where it has translucent membrane which is not associated with visual distortion or retinal distortion. Grade 1 is membranes or crinkled cellophane maculopathy where the membrane causes irregular wrinkling if inner segment of retina, increased vascular tortuosity and peri macular vessel being pulled towards the fovea. Grade 2 is membrane or macular pucker. It is an opaque and thick membrane that causes profound wrinkling of the retinal architecture. It may associate with features such as cystoid macula oedema, intra-retinal hemorrhages or shallow retinal detachment [4].

Sidd RJ et al. shows that prevalence of ERM is much higher in Asian population in comparison with Caucasian. General prevalence of idiopathic epiretinal membrane is around 6-7% [5]. Prevalence of Idiopathic ERM increases exponentially with age. The prevalence around 1.9% for age below 60 years, 7.2% 60-69 years, 11.6 70-79 years and 9.3% above 80 years old, while it is bilateral in 10-30% of cases [2,5]. There is slight predominance of incidence among female in comparison with male [5].

There are few identified risk factors involved in development of idiopathic ERM such as older age, female gender, myopia and hyperlipidemia [6]. Pathophysiology for idiopathic epiretinal membrane is still controversial and exact types and origin of cells that make up different type of ERM are still debatable[7-8].

However, proposed pathophysiology for idiopathic ERM primarily glial origin meanwhile secondary ERM originates from multiple cells from inner retina such as retinal pigment epithelium (RPE), fibroblast and macrophages [9-10]. In addition, Posterior Vitreous Detachment (PVD) also plays important role in formation of idiopathic ERM as its present in 90% of idiopathic ERM eye and almost all retinal detachment or retinal break eye [11]. It is said that due to detachment, there is micro break in Internal Limiting Membrane (ILM) and leading to migration of glial cells to the inner aspect of retina and causing proliferation resulting in the formation of idiopathic ERM [8].

On contrary, another study proposes that the residual cortical vitreous following vitreous detachment causing formation of idiopathic epiretinal membrane[12]. In non PVD eye, it is proposed that migration of glial cells through pre-existing ILM break or thinned ILM [13]. In contrast, secondary epiretinal membrane due to retinal detachment or retinal break is due to presence of retinal pigment epithelium in vitreous cavity causing proliferation in the retinal surface.

ERM disease progression can be classified into three, regress, stable and progression. According to Blue Mountain Study, progression was seen in 28.6% cases, stable in 38.8% and in 25.7% of cases regressed[14]. It tends to have no progression or limited progression. Hence most patients are asymptomatic or have mild symptoms.

Only about 10-25% of cases that has impaired visual acuity and those visual acuity worse than 20/200 account less than 5%[3-4][15]. Astonishingly, there were cases reported as spontaneous separation of ERM with improvement of visual acuity[16]. The majority of ERM patients are asymptomatic as mentioned earlier. They belong to Grade 0 cellophane maculopathy. It only becomes symptomatic when it involves macula and peri-macula areas.

They usually complain of reduced visual acuity, metamorphopsia, micropsia or even monocular diplopia [17]. The decrease in visual acuity can be attributed to traction of the vitreo-retina, cystoid macula oedema or thickness of the ERM itself. The wrinkling effect of the retina produces metamorphopsia.

Diagnosis of this disease is mainly via clinical and supplemented by investigation such as Optical coherence tomography to assess the severity. Occasionally additional testing such as Fundus Fluoresceine Angiography is needed. In the early phase, mild glistening can only be seen. In more advanced cases, there will be gross wrinkling or striation with gross retinal vasculature distortion. Other clinical findings may be visible via indirect ophthalmoscope such as intra-retinal hemorrhages, central macular oedema, retinal break, posterior vitreous detachment or even pseudo holes.

OCT on the other hand is sophisticated and the most crucial tool in diagnosis, assessing severity and complication for ERM. It helps in identifying ERM where it shows as hyperreflective layer over innermost surface of the retina. It also helps in identifying complications such as cystoid macula oedema or even macula hole. They help very much with pre-operative and post-operative assessment tools.

1.2 OPTICAL COHERENCE TOMOGRAPHY (OCT) in ERM

Optical coherence imaging (OCT) has been an indispensable imaging modalities in ophthalmology because of the intricate, thin structures of the retina [18]. Since its introduction, OCT has become an essential tool for research, screening, diagnosing, and monitoring diseases of the macula and optic nerve head. In ERM cases. It is a tool that produces non-invasive high-resolution cross-sectional images of biological tissues. It has been proven that its more sensitive than conventional method of clinical diagnosis [17].

Emergence of SD OCT has given the ability to provide high resolution and enables analysis by allowing 3-dimensional imaging, thereby enhancing the picturization of the intraretinal architectural morphologic features [19]. It has been vital to vitreo-macula interface pathology to classification of ERM based on oct findings has been published.

OCT based idiopathic ERM has been classified based on morphology of the fovea. The proposed classification is (1A) fovea-involving ERM with outer retinal thickening and minimal inner retinal change, (1B) fovea-involving ERM with outer retinal inward projection and inner retinal thickening, (1C) fovea-involving ERM with prominent thickening of the inner retinal layer, (2A) fovea-sparing ERM with formation of a macular pseudo hole, and (2B) fovea-sparing ERM with schisis-like intraretinal splitting.
(Figure 1) [20].

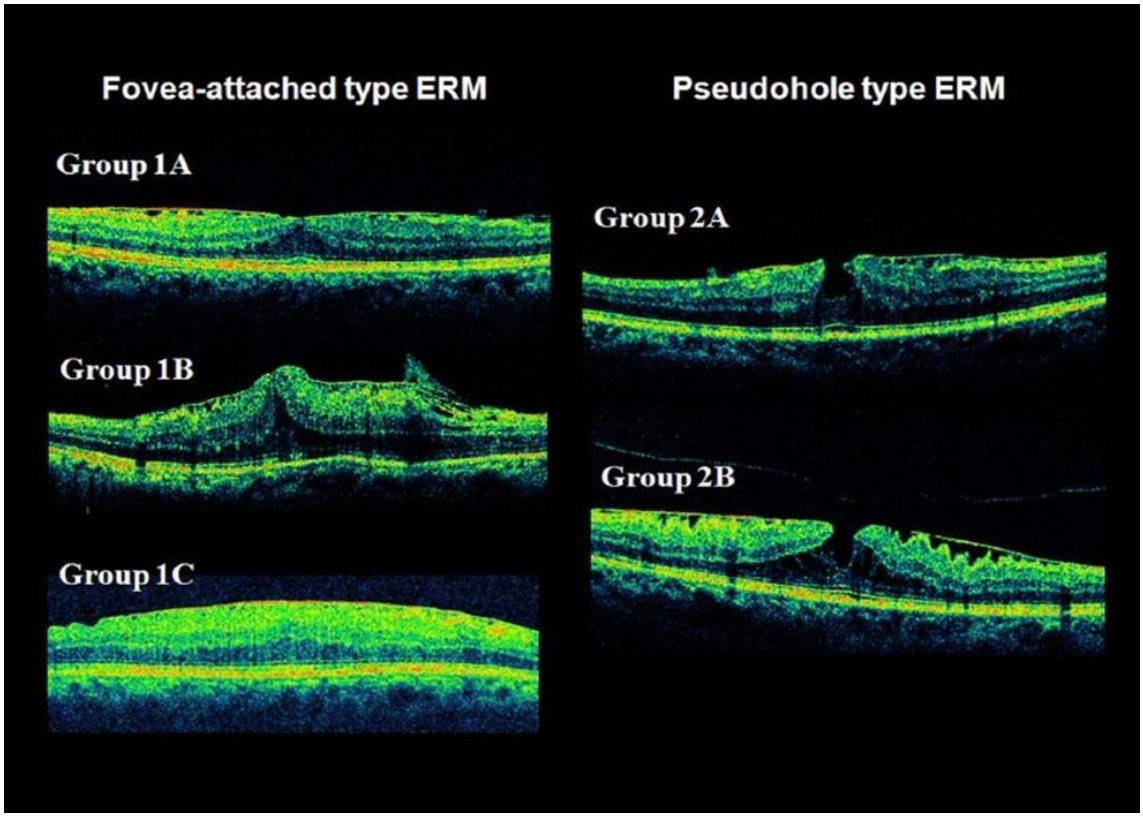

Figure 1: SD-OCT classification of idiopathic epiretinal membrane.

Similarly, there is another proposed OCT based ERM classification which is more in detail. The proposed idiopathic classifications include (A) with PVD and (B) without PVD. Classification (A) was subclassified as (A1) without contraction of the ERM and (A2) with contraction of the ERM; subclassification (A2) was further subclassified as (A2.1) with retinal folding, (A2.2) with oedema, (A2.3) with cystoid macular oedema, and (A2.4) with lamellar macular hole. Classification (B) was subclassified as (B1) without VMT and (B2) with VMT; subclassification (B2) was further subclassified as (B2.1) with oedema, (B2.2) with retinal detachment, and (B2.3) with schisis. (Figure 2) [21].

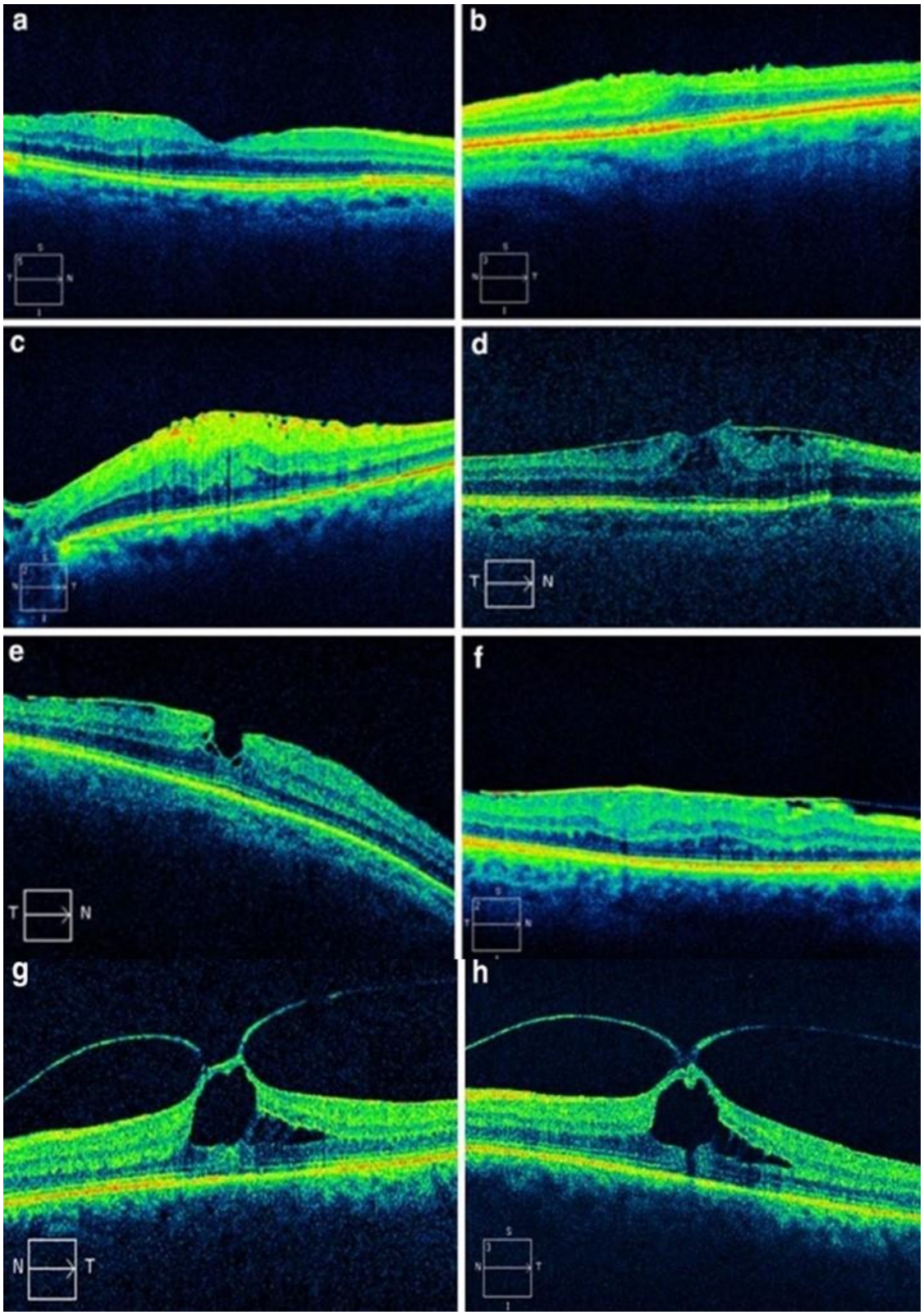

Figure 2: Epiretinal membranes with posterior vitreous detachment without contraction (a), with folding (b), with edema (c), with cystoid macular edema (d), and with lamellar macular hole (e). Epiretinal membranes with vitreous attachment without traction (f), with VMT and the presence of edema (g), and with schisis (h)

OCT- spectral domain also can be used in measuring other parameters such as central retinal thickness. It is measured from innermost aspect of the retina to the retinal pigment epithelium layer at fovea [22]. They have been a measuring point to assess pre and post epiretinal membrane surgery. Central sub-foveal thickness measurement varies with OCT machines. The central subfield thickness range is 220.5-294.8μm.

In post-operative assessment it can also help in detecting complications such as macula hole and pseudo hole. Furthermore, OCT helps in identifying Inner Segment (IS) and Outer Segment (OS) junction integrity. It predicts the visual outcome postoperative in patients with Epiretinal Membrane [23]. IS/OS junction integrity has been under study recently as a strong visual outcome predictor for various retinal diseases. Its classically defined as the junction between photoreceptor inner segment and outer segment [24].

It has been reported as disrupted junction is associated with low visual acuity in retinal vein occlusion patients [24]. Besides the fact that it helps preoperative assessments OCT also helps in assessing the outcome of the surgery post-surgery. Detection of changes in the IS/OS junction, central subfield thickness and presence of complications such as macula hole or retinal detachment can identified using OCT [25].

In recent times, due to the advancement of OCT imaging techniques researchers have been studying detailed assessment of inner retina morphology named as Disorganized Retinal Inner Layer (DRIL). DRIL as the name implies is the boundaries of the ganglion cells, inner plexiform, and outer plexiform layer that cannot be delineated well [26]. It has been an important prognostic marker for poor visual outcome in macula oedema most notably due to diabetic retinopathy and retinal vein occlusion [26-27].

Some researchers have gone till the extent of measuring the horizontal extend of the DRIL as well presence of DRIL post treatment to analyze this new robust OCT biomarker [28-30]. Hence taken all account together, DRIL appears to be a reliable poor visual outcome biomarker for vitreo-retina interface as well inner retinal pathology.

Central subfield mean thickness (CST) in contrary have been used as tools for biomarker for retinal diseases such as macula oedema, macula hole and epiretinal membrane. As the name implies, it is the distance between the inner surface of the retina and the inner surface of the retinal pigment epithelium as measured at the central fovea. It can be either called center point thickness or central subfield mean thickness. It is measured as circular area of diameter 1 mm centered around the center point. About 128 thickness measurements are made in this circular area and the mean value is obtained [31].

Although these measurements are highly correlated, central subfield mean thickness is preferred because it is the average of more data points and is less dependent on scan centration [31]. CST value varies according to age, sex, distance from center fovea and even the type of OCT machine [32-33]. The average CST is around 257.6±19.6 μm and it has shown spectrum domain based OCT has shown better than time domain OCT [33]. This biomarker has shown has good correlation between increased CST and poor baseline visual acuity [22-23]. However, inconsistent correlations between preoperative CST and postoperative visual acuity. Hence, its suggestive that CST may be a good predictor for baseline visual acuity but may not be ideal for post operative predictor visual acuity [34].

1.3 EPIRETINAL MEMBRANE SURGERY

Epiretinal membrane removal gold standard treatment is via surgery. Pars plana vitrectomy with membrane peeling has been mainstay surgical treatment since 1978 [35]. In early 80's large gauge vitrectomy was the first to be explored, however, from 2004 small gauge (23-25-27) instruments became widely used [36].

The vitrectomy surgery involves a standard three-port pars plana vitrectomy using 23-gauge instruments. Core vitrectomy was done first followed by detachment of posterior hyaloid around the optic nerve head by active aspiration with a vitrectomy probe. Next using a vitreoretinal pick or bent microvitreoretinal blade, edge of the epiretinal membrane is picked, which was then grasped with the intraocular forceps, separated from the underlying retina, and removed from the eye.

After the removal of the ERM, dye is injected to stain Internal Limiting Membrane (ILM) and will be removed. Among the types of dyes used for macular surgery, now, indocyanine green has been withhold from usage as it causes in-vitro and in-vivo toxicity concerns [37-38]. Trypan blue and brilliant blue are generally well accepted due to safety profile and have good affinity towards ERM and ILM [39-40]. At the end of surgery, the peripheral retina was examined with scleral depression to search for retinal tears and dialysis.

The concept of ILM and ERM peel concept is based on removing tangential forces acting upon the inner retina leading to revert the distorted retinal architecture at vitreo-retina interface [41]. Since the introduction of PPV treatment for ERM, it has shown tremendous success rate in anatomical restoration however, visual outcome still variable [42-44]. This could be attributed due to many factors related to the surgery itself. The safety related issues have been somewhat prominent issues to be noted.

In general, general complications related to PPV itself are such as iatrogenic retinal breaks or retinal detachment. It has been reported incidence rate of occurrence around 1.7% to 11% after surgery for ERM [45]. Secondly, cataract formation in lens sparing PPV is a well-known cause. Its occurrence is found to be higher in older age population and either 20-gauge or 23-gauge incision PPV [46-47]. These complications can be overcome by combining phaco-vitrectomy at single setting or by performing cataract surgery later in two stage operation.

Open-angle glaucoma and increase of intraocular pressure (IOP) in the acute postoperative period is a essentially known effect, which may be related to various causes such as buckling procedures, laser photocoagulation, use of tamponades, intraocular steroids, hemorrhages, and inflammation [48]. Endophthalmitis accounts for minute 0.05%-0.07% occurrence due surgery for ERM. Be it with suture or suture less surgery, the is no significant statistical differences noted in the occurrence of post-PPV endophthalmitis [1,49-50].

Specific to ERM procedure related risks are such as swelling of arcuate nerve fibers (SANFL) and dissociated optic nerve fiber layer (DONFL). This is attributed by development of technique of ILM peel with ERM peel in ERM surgery [51-52]. To prevent recurrence of ERM, ILM peel has been widely used. It has proven that produce favorable outcome in preventing recurrences however doubtful in functional aspects [35].

Due to peeling of ILM, the vicinity structures such as retinal nerve fiber layers and inner segments of the retina are vulnerable to iatrogenic damage. Due to damage to inner retina and Muller plate, formation of arcuate striae formation at macular region accounted for about 31% in ILM-peeled eyes [53-54]. This SANFL reported to resolve completely on its own within 3rd month and does not affect visual acuity reduction. Similarly, DONFL occurrence is about 31% 3 months post-surgery and due to damage to Muller cells and it does not associated with any visual loss [55].

1.4 RATIONALE OF STUDY

The efficacy of surgical treatment for ERM has been extensively studied and is currently unanimously approved. ERM surgery is generally recommended when blurred vision or vision distortions are severe enough to interfere with binocular vision or daily activities. The challenge in this era is correct and profitable surgical indications. Surgeons must tailor each patient individually to the subject for surgery or best if leave it under observation.

Hence, this study is aimed to investigate the outcome of ERM surgery by comparing prognostic parameters using preoperative visual acuity, duration of symptoms and OCT imaging biomarkers between observational and interventional group. Therefore, it may reduce the burden to surgeon by helping to prognosticate every patient prior surgery and minimize patient to be subjected to over-zealous intervention of vitrectomy surgery.

Finally, as far we know there is no available data or reports in Malaysia that focuses on the comparison on anatomical and functional outcome of ERM surgery. By gathering data in this study, we anticipate the resulting data could benefit the healthcare system at large particularly in vitreo-retina fraternity in Malaysia.

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Chapter 2

Objective

2. STUDY OBJECTIVES

2.1 GENERAL OBJECTIVE

To evaluate anatomical function and visual function outcome of idiopathic Epiretinal Membrane (ERM) between observation group and intervention group at 6-month post-operative.

2.2 SPECIFIC OBJECTIVES

1. To compare the anatomical outcome of idiopathic ERM Central sub-foveal Mean thickness (CST), Ellipsoid zone integrity (EZ) and Disorganized Retinal Inner layer (DRIL) between observational and intervention group at 6-month post-operative.

2. To compare visual function outcome (visual acuity) between observational and intervention group at 6-month post-operative.

3. To identify the association between the duration of ERM with visual function outcome of surgery.

Chapter 3:
Manuscript