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Assessing the outcome of inner limiting membrane peeling in treating idiopathic epiretinal membrane

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ASSESSING THE OUTCOME OF INNER LIMITING MEMBRANE PEELING IN TREATING IDIOPATHIC EPIRETINAL MEMBRANE

by

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DEDICATION

I would like to dedicate this project to all the kind-hearted and wonderful patients that made my time at the clinic pleasant and memorable. The ones that have encouraged me and inspired me to be the best that I can be. Thank you all!
ACKNOWLEDGMENTS

I would like to express my sincerest gratitude towards Dr. Jorge G. Arroyo who accepted me as a member of his healthcare and research team. It was truly a privilege to have been given the opportunity to work with one of the most humble, caring, and intelligent people that I have ever met. Dr. Arroyo is an amazing mentor and an extraordinary role model. I would also like to mention Gina Yu, one of the most hardworking, driven, and kind people that I have ever had the pleasure of working with. She inspires everyone around her and I wish her success in her endeavors in the medical field.
ASSESSING THE OUTCOME OF INNER LIMITING MEMBRANE PEELING IN TREATING IDIOPATHIC EPIRETINAL MEMBRANE

ARIA BASSIRI

ABSTRACT

Idiopathic Epiretinal membrane is a proliferation of contractile cells on the surface of the retina that typically occurs after posterior vitreous detachment. Though many questions have been raised on the causes of this condition, a greater debate has been on the treatment of this pathology. The literature suggest the potential benefit in peeling ILM, due to its inherent proliferative characteristics, along with the ERM, during the surgery, however sufficient data has yet to been found. Due to the lack of consensus in treatment of iERM, this study set forth to provide some insight on the surgical outcomes of patients that undergo combined peeling as well attempting to contribute to a potential surgical protocol in treating iERM. This was a retrospective case series study looking at 140 eyes from 126 iERM patients that underwent ERM surgical treatment at Beth Israel Deaconess Medical Center between 1998 and 2015. Pre- and post- operative visual acuities, lens status (phakic, aphakic, pseudophakic), type (kenalog with or without ICG) and duration (0.5min, 1 min, 1.5 min) of the stains used in the procedure, and any prior or successive surgeries were recorded and analyzed. Overall, ERM
surgeries demonstrated a significant (p<0.0001) improvement in visual acuity. Furthermore, the combined peel patients demonstrated a significantly (p<0.0467) greater mean change in logMAR score when compared to ERM-only peel procedures. In addition, the combined peel group showed a smaller rate of recurrence. Lastly, simultaneous cataract surgery and the use of ILM stains did not have an impact on the outcome of ERM surgery. The study found that combined (ERM and ILM) peeling along with simultaneous cataract surgery, if a cataract was present, along with the utilization of ILM stains is cost-effective, safe, and effective approach in treating iERM and decreasing its recurrence.
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LIST OF ABBREVIATIONS

CFT ................................................................. Central Foveal Thickness
CNS .............................................................. Central Nervous System
ERM ............................................................. Epiretinal Membrane
FA ................................................................. Fluorescein Angiography
FTMH .......................................................... Full-Thickness Macular Hole
ICG ............................................................... IndoCyanine Green
iERM ........................................................... Idiopathic Epiretinal Membrane
ILM ............................................................... Inner/Internal Limiting Membrane
IOL ............................................................... IntraOcular Lense
LogMAR ....................................................... Logarithm of the Minimum Angle of Resolution
ME .............................................................. Macular Edema
MPH ............................................................. Macular PseudoHoles
MRI ............................................................. Magnetic Resonance Imaging
OCT .............................................................. Optical Coherence Tomography
PPV ............................................................. Pars Plana Vitrectomy
PVD ............................................................. Posterior Vitreous Detachment
RNFL ........................................................... Retinal Nerve Fiber Layer
RPE ............................................................. Retinal Pigment Epithelium
SEM ............................................................. Standard Error of the Mean
INTRODUCTION

They human eye is one of the most complex and intriguing structures in the body. From its unique evolutionary implications to its unique yet fascinating embryological development, the human eye has been one of the most studied and sought after structures in the human body. It is often one of the first structures to be damaged during a systemic disease but may also be independently affected by unique and complex conditions. With the ongoing surge of systemic conditions in the general population, such as metabolic syndrome, the eye has been studied very closely to be better understood and to establish more effective and efficient interventions to deal with ocular pathologies.

The Structure of the Human Eye

The eye can be broadly categorized into two segment: the anterior segment and the posterior segment (Kolb, 1995). The anterior segment can be further divided to the anterior chamber and the posterior chamber (Kolb, 1995). The anterior chamber contains the cornea, aqueous humor, and the Iris, while the posterior chamber includes anything between the iris and the vitreous humor which includes the lens (Kolb, 1995). The posterior segment comprises the vitreous humor, retina, choroid, and the optic nerve (Kolb, 1995). The anatomy of the main eye structures is depicted in Figure 1.
Figure 1: **Structure of the eye.** This is a crude diagram of the main structures in the eye. The cornea, lens and iris within the anterior chamber of the anterior segment. The lens in the posterior chamber of the anterior segment. Within the posterior segment, the retina, choroid, optic nerve are present. Not labeled is the vitreous humor which lies in the space between the retina and Iris. Figure taken from (Kolb, 1995).

**Retina**

As the light emerges towards the anterior segment of the eye, it is refracted through the cornea and the lens on to the retina, where the information is translated and transported via the optic nerve in to the central nervous system (CNS) to be further analyzed (Kolb, 1995). Accordingly, the retina has multiple layers and is a crucial component of the eye not only converting the light signal but also relaying it on to the optic nerve (figure 2).
Figure 2: Layers of the retina. The intricate organization of the retina is depicted. Light would be emerging from the bottom of the image, traveling through the inner limiting membrane towards the pigmented epithelium. The light is then converted to electrical input at the rods and the cones and is transported through the neural cells to the optic nerve. More broadly, the layers can be divided to neural retina and the retinal pigment epithelium. Furthermore, The choroid nourishes the retinal pigment layer and a portion of the neural retina, while the retinal arteries provide nourishment for the remaining neural tissue of retina. Figure taken from (Kolb, 1995).

Also depicted in figure 2, are the photoreceptors, rods and cones, which have differential distributions throughout the retina. These photoreceptors are responsible to convert light into electrical energy which can then be transported to the CNS to be processed (Kolb, 1995). The rods responds to the less intense light but are more sensitive than the cones, which are responsible for color vision.
and higher intensity light. Notably, the cones have the highest density in the fovea, which is located at the center of the macula. The macula, approximately 5.5 mm in diameter, contains the fovea (approximately 1.5 mm), a region of the retina which provides the highest visual acuity (Kolb, 1995). Figure 3 depicts the aforementioned structures in a fundus photo, a photo taken from the interior surface of the posterior segment of the eye. In turn, damage to this region of the retina will have the most significant impact on one’s vision.

**Figure 3: A fundus photo of the left eye.** The macula and the fovea are both labeled on the diagram. Figure taken from (Willoughby et al., 2010).

Interference with any aspects of this intricate system, responsible for guiding, translating, and transporting the light, will impact the vision. Particularly, pathologies that impact the retina can significantly hinder visual acuity. Such pathologies include but are not limited to fluid or blood accumulation, irregular
tissue growth, accumulation lipids or other macromolecules, consequently all act to interfere with the proper functioning of the retina. A huge area of interest in treating such conditions is focused on interventions involving the inner limiting membrane (ILM), discussed later. Clinically, such interventions have shown potential to be applied in surgical procedures treating macular holes and epiretinal membrane however the potential impact and prognosis must be closely monitored.

Epiretinal Membrane (ERM)

First documented by Iwanoff in 1865, Epiretinal membrane (ERM) is a contractile fibrotic membrane, composed of extracellular matrix, that develops at the vitreo-retinal junction (Tsilimbaris, Tsika, Kontadakis, & Giarmoukakis, 2016). ERM can be classified into two categories: 1) primary or idiopathic ERM (iERM) 2) secondary ERM. As the name suggests, iERMs are diagnosed when no underlying cause has been determined and evidence suggest the spontaneous formation of the fibrotic layer over the retina (Bu, Kuijer, Li, Hooymans, & Los, 2014). On the other hand, ERMs may be secondary to other causes such as various retinal vascular and inflammatory diseases, trauma, retinal breaks, tears, or detachments, and also present in patients with a history of previous retinal surgery (Tsilimbaris et al., 2016). Although the two subtypes of ERM share a common endpoint, the specific origin of cell that initiate the process of the scar tissue formation has not been fully elucidated. Literature suggest that the iERM
have cells that originate from the neural retina, in contrast to the secondary ERM which likely do not have cell with neural origin, and potentially originate from retinal pigment epithelial (RPE) cells (Tsilimbaris et al., 2016).

Of the different categories ERM, the most prevalent appear to be the iERM and ERMs associated with retinal tears or detachment or their associated surgical treatments (Mitchell, Smith, Chey, Wang, & Chang, 1997). Furthermore aging is found to be a significant risk factor in patients with iERM (Klein, Klein, Wang, & Moss, 1994). Interestingly, The prevalence of iERM has shown to increase above the age of 60 peaking between the ages of 65-75 (Klein et al., 1994).

Pathogenesis

The pathogenesis of iERM has been heavily linked to posterior vitreous detachment (PVD) as they are often present 80-95% of the cases (Appiah, Hirose, & Kado, 1988; Kishi & Shimizu, 1994; Sidd, Fine, Owens, & Patz, 1982). PVD is a condition associated with the separation of the vitreous from the ILM of the retina often associated with age but may also be secondary to other retinal conditions (Johnson, 2010). Figure 4 visualizes PVD in its different stages.
Figure 4: Progression of PVD. This illustration depicts PVD and its progression through its stages. Stage 1 is a perifoveal detachment with residual vitreofoveal traction. Stage 2 is a complete perifoveal detachment. Stage 3 is near complete PVD. Lastly, Stage 4 is a complete PVD. Figure taken from (Johnson, 2005).

The current pathogenesis theory for iERM suggests that the neural cells, likely glial cells, are able to migrate through the ILM breaks into the pocket created as a result of the PVD where they are able to proliferate into a sheet, due to the favorable proliferative environment created by ILM (Bu et al., 2014; Tsilimbaris et al., 2016). However this hypothesis fails to account for the cases of iERM that do not present with PVD but these cases probably have an undetected partial PVD with separation of vitreous from retina at the macula. A similar mechanism has been suggested for the secondary ERM, where in place of PVD,
a retinal tear or detachment, previous retinal interventional procedure, or damage to the retina, allow passage of cells without neural origin to find their way on to the surface of ILM where they are able to proliferate into a sheet (Bu et al., 2014; Tsilimbaris et al., 2016). More recent studies have elucidated the potential contribution of growth factors and inflammatory cytokines, such as nerve growth factor, glial cell line-derived growth factor and transforming growth factor B1, as they relate to ERM formation (Joshi et al., 2013).

**Diagnosis**

Although ERM may present asymptomatic in some patients, when thin and translucent, its progression into a thicker and more opaque membrane may lead to a decline in visual acuity and macular disturbances. Often ERMs that develop on the macula, more specifically in the fovea, will be more symptomatic as they are interfering with the region of the retina responsible in providing the greatest visual acuity and in turn will require treatment. The impact on vision is primarily affected by location, transparency, and thickness of the developed membrane.

Clinically, the diagnosis of an ERM can be done through a dilated fundus examination or fundus photograph to identify the presence of the membrane (Tadayoni et al., 2001). During the examination, depending on severity, a greyish membrane may be seen along with some macular or retinal vasculature distortion due to the contractile characteristics of this tissue (figure 5) (Tadayoni
et al., 2001). Moreover, diagnosing iERM is a diagnosis of exclusion, where a complete examination must rule out any other causative factors such as retinal vascular and inflammatory diseases, trauma, retinal breaks, tears, or detachments, and also a history of previous retinal surgery.

**Figure 5: A fundus image of the right eye depicting ERM.** The macula is located in the center of the image. Upon closer inspection some distortion of the macula as well as the vasculature can be seen which is primarily caused by the contractile property of the ERM. Figure taken from (Tadayoni et al., 2001).

Furthermore, Optical Coherence Tomography (OCT) is a more definitive diagnostic tool used. OCT is a noninvasive imaging technique which utilizes near infrared light to capture micrometer-resolution images (Huang et al., 1991). OCT can be used to create cross sectional images of the retina to allow for qualitative and quantitative analysis of the retina (Figure 6) (Hee et al., 1995).
Figure 6: Sample labeled OCT image. The identifiable structures include the Fovea, vitreous, optic disc, choroid, sclera, and Retinal nerve fiber layer (RNFL). Clinically, anatomical changes in these layers can be quantitatively and qualitatively analyzed. Although not shown in this image, pathologies such as edema, ERM, macular hole, and many other structural pathologies may viewed by utilizing OCT images. Figure taken from (Hee et al., 1995).

The use of OCT allows for the visualization of the ERM as well as the other clinical features that are often associated with it. Macular Edema (ME) and macular thickening are often associated with the decreased vision in ERMs and these can also be measure and visualized through the OCT images (Folk et al., 2015; Wilkins et al., 1996) (Figure 7).
Figure 7: OCT of a patient with ERM. The thin ERM lies directly on top of the retina. Notably a PVD is also present which looks like faint green line running across the top portion of the image. This line is the border of the vitreous and the OCT image depicts its separation from the retina. Figure taken from (Johnson, 2010).

It should be noted, the use of OCT is not limited to diagnosing ERMs and it is a very useful and efficient tool to diagnose other retinal pathologies including macular holes, Age related macular degeneration, central serous retinopathy, diabetic retinopathy and etc. Additionally, the OCT may used to distinguish between Macular Pseudoholes (MPH) and Full-Thickness Macular Holes (FTMH) (Lowe & Gentile, 2013). Pseudoholes are created as a consequence of the contractile properties of ERM. In turn, the contractions lead to the folding of the retina which may appear as a FTMH. The feature that distinguishes them from macular holes is that the layers of the retina are not defected. This distinguishing feature can be easily observed in an OCT image (Fig 8).
Figure 8: OCT of Macular Pseudohole and FTMH. The OCT image at the top is a patient with ERM and pseudohole while the patient on the bottom has a Full thickness stage 3 macular hole. After examining the retina, it is evident that the patient with the pseudohole does not have a defect in any of the retinal layers while the patients suffering from the FTMH has defects across all the layers. Figure taken from (Lowe & Gentile, 2013).

As an Ancillary test, Fluorescein Angiogram (FA) may also be used to obtain more information. In this imaging technique, Fluorescein dye is injected in the blood stream and as it travels through the vasculature of the eye, images are taken. FA allows for the visualization of any leakage or pooling of fluid, presence of any vessel distortion or vascular changes, and can help exclude any other retinal conditions during the differential diagnosis (Folk et al., 2015).

Using the diagnostic tools, ERM can be further categorized by a grading system. Gass has proposed a grading system to differentiate ERMs at its different stages (Agarwal & Gass, 2011).
Grade 0 membranes are also referred to as cellophane maculopathy. These membranes are transparent and do not cause any visual changes. As these membranes are asymptomatic they may be found incidentally during a routine exam.

Grade 1 membranes are also referred to as Crinkled cellophane maculopathy. These membranes cause irregular wrinkling in the inner retinal layers due to their inherent contractile properties. As expected this may also cause distortion of vessel. Unlike cellophane maculopathy, these membranes may be symptomatic, especially when the fovea is the affected region. It should be noted that the visual disturbances are due to the retinal distortions and not due to the opacity or thickness of the membrane.

Grade 2 membranes are also referred to as macular pucker. These membranes are thick and more opaque. Furthermore, these membranes cause vasculature and full thickness retinal distortion and are often associated with exudate and macular edema. Its been reported that approximately 80% of these patients will have symptoms (Wickham & Gregor, 2013). These symptoms include blurred vision or metamorphopsia. FA studies can be used to study the location and the severity of the edema. Lastly, Severe ERM contractions can lead to cotton wool spots (Arroyo & Irvine, 1995). Cotton wool spots are small, white/grey, cloudy, fimbriated-edged lesions that appear to float in a fundus examination. These lesions are accumulations of intracellular product caused by damage to the nerve fibers. Severe contractions by the ERM may lead to ischemia or blockage of the
axoplasmic flow and subsequently damage to the nerve fiber layer (Arroyo & Irvine, 1995).

It is noteworthy to add that iERM is a chronic disease with slow onset and progression. Accordingly, In a 5 year study it was found that the cumulative progression rate from the least severe to the most severe was at 9.3% (Fraser-Bell, Guzowski, Rochtchina, Wang, & Mitchell, 2003). In addition, the study found that the overall the progression was at 28.6%, while 25.7% showed regression and lastly, 38.8% remained stable (Fraser-Bell et al., 2003). The slow progression of this condition have further been reaffirmed by other studies (Charlap et al., 1992; Hayashi & Hayashi, 2008).

**Treatment**

Observation or surgical interventions are both treatments options for iERM. This is strongly dependent on the severity or the grade of ERM and whether the ERM is symptomatic. The current clinical standard in treating iERM is pars plana vitrectomy (PPV) operation with ERM peeling. PPV, first introduced by Machemer in 1972 is the standard surgical intervention used in treating vitreoretinal pathologies, such as macular holes (Bu et al., 2014). Due to the complications associated with PPV, discussed later, there have been studies that suggested ERM peeling without PPV, however the standard ERM peeling is typically done proceeding a PPV (Reibaldi et al., 2015; Sawa et al., 2001). The PPV is performed to separate the posterior cortical hyaloid from the retina, in
others words create a complete PVD. Once the posterior hyloid is completely separated from the retina, ERM can be peeled and removed from the eye. Figure 9 illustrates preoperative and postoperative OCT images of a patient that underwent successful PPV with ERM peel.

Figure 9: Preoperative and Postoperative OCT of iERM patient. The top is a preoperative OCT of a patient with ERM which is directly covering the fovea which was symptomatic. At the bottom, is a 3 month post operative OCT of a patient that underwent PPV and ERM peel. Figure taken from (Suh, Seo, Park, & Yu, 2009).

PPVs are often done with smaller gauge systems because they are sutureless and atraumatic. More recently with the introduction of 23G, 25G, and 27G more options are given to surgeons (Oshima, Wakabayashi, Sato, Ohji, & Tano, 2010). The choice is primarily dependent on the surgeons preference as they do not seem to have an impact on postoperative outcomes (Grosso et al.,
2014; Haas et al., 2010; Kusuhara et al., 2008; Sandali et al., 2011). However, surgeons often utilize smaller gauges because they offer better postoperative comfort resulted from less surgical trauma.

**ILM peel**

It has been proposed that the removal of the ILM should accompany the conventional ERM surgery. The ILM is the most superficial layer of the retina, at the junction between the retina and the vitreous humor. Histologically, the ILM is composed of laterally contacting Muller cells feet and basement membrane components, such as collagen IV (Semeraro et al., 2015). Due to its composition, it is believed that the ILM provides a favorable proliferative environment. Notably, the spontaneous separation of the ILM in Terson’s syndrome, has shown no subsequent fibrosis in the macula or decline in visual acuity highlighting a potential therapeutic use with intentional peeling when treating fibrocellular proliferative conditions of the retina, particularly at the vitreo-retinal junction (Kuhn, Morris, Witherspoon, & Mester, 1998; Morris, Kuhn, Witherspoon, Mester, & Dooner, 1997). Thus, due of its location and inherent characteristics it is believed that the ILM may be involved in the pathogenesis or recurrence of various vitreoretinal diseases, such as macular holes and different subtypes of ERM.

The intentional removal of ILM is potentially cost-effective and has shown a significant success rate in surgical treatment of macular holes (Lois et al.,
2011; Ternent et al., 2012). Consequently, it has been implemented into the conventional surgical treatment of ERM and has shown an improved success rate (Park et al., 2003; Semeraro et al., 2015). Despite the potential benefit of implementing ILM peeling, the surgeon must overcome two major obstacles. The first is the potential risk of damage to the retina, which lies directly underneath the ILM, during the peeling process. Furthermore, due to its transparency it is difficult for the surgeon to locate ILM with the naked eye. To overcome this obstacle, specific stains such as Indocyanine green dye (ICG) are used during the surgery in order to stain this layer (Semeraro et al., 2015). The use of ICG allows to selectively stain the ILM layer to be distinguished from the other structures present. Aside from ICG, other stains such as trypan blue and Brilliant Blue G have emerged, with varying selectivity and toxicity, and are also used to stain the ILM.

Complications

Generally, PPV surgeries are common and safe procedure in treating vitreoretinal pathologies. However, this procedure may be associated with some intraoperative and postoperative complication. The most frequent postoperative complication is the development of cataracts in phakic eyes that had undergone a vitrectomy. Typically, there is an improvement in the visual acuity within the first few months however this is followed by slowly developing cataracts which leads to a decrease in visual acuity and the need for a second operation. Due to this
high incidence rate of cataract development surgeons often elect combine ERM surgeries with phacoemulsification and intraocular lens (IOL) placement in order to eliminate the need for a second operation (Chuang et al., 2012; Lee, Cheng, & Wu, 2011; Moisseiev et al., 2012; Yiu et al., 2013). Although rare, other complications include intraoperative retinal tears, postoperative retinal detachment, hemorrhage, or infection (Carter, Michels, Glaser, & De Bustros, 1990; Cohen, Flynn, Murray, & Smiddy, 1995; Eifrig, Scott, Flynn, Smiddy, & Newton, 2004; Ghoraba & Zayed, 2001; McDonald, Verre, & Aaberg, 1986; Sharma et al., 1997; Sjaarda, Glaser, Thompson, Murphy, & Hanham, 1995).

**Surgery versus Observation**

Due to the many benefits and complications associated with the ERM surgery, there has been a great debate on whether observation or surgical interventions should be chosen as a treatment plan. On the one hand, the surgery has shown to be a safe and effective intervention to improve and stabilize vision (Chuang et al., 2012; Falkner-Radler, Glittenberg, Hagen, Benesch, & Binder, 2010; Kinoshita et al., 2012; Lee et al., 2011; Moisseiev et al., 2012; Thompson, 2004). In contrast, the slow progression of the condition, discussed earlier, coupled with the potential complications associated with the surgery, may discourage patients from electing the surgical intervention. In addition, most improvement in vision after surgical intervention has been observed with patients with lower visual acuity preoperatively, however, the
higher visual acuity is observed in patients with better preoperative visual acuity (Pesin et al., 1991; Song, Kuriyan, & Smiddy, 2015). Lastly, there is also no consensus on the optimal time to treat the condition. Thus as the surgeons and patients discuss treatment plans, all the aforementioned factors should be considered.
Specific Aims and Objectives

Due to a lack of consensus on the appropriate treatment plan and surgical goals of ERM, this study sets forth to investigate the surgical outcome of ERM treatment. Specifically, the primary goal of this study is to investigate the surgical outcome of patients with iERM. This study aims to analyze the prognosis of patients that underwent ERM-only peel surgery and compare them to patients that underwent ERM and ILM peeling. With the presence of inconclusive evidence in current literature, this study aims to shed some light on the matter by attempting to recognize the surgical procedure possessing the greater efficacy in treating iERM. Furthermore, the current study aims to determine the potential impact of simultaneous cataract surgery and preoperative lens status (phakic versus pseudophakic) on visual outcomes postoperatively. Lastly, with the emerging use of ILM staining dyes in surgical interventions treating various vitreoretinal junction pathologies, concerns have been raised on the potential toxicity of these dyes and their possible impact on the surgical outcome. In turn, this study will investigate this matter by comparing the outcomes of surgical cases that utilize ILM stains with ones that are undertaken without them. This study will further explore this question by evaluating a possible correlation between the duration of dye use and postoperative results. Collectively, the goal of this study is to provide some insight and statistical evidence on treatment of iERM.
METHODS

In this study we analyzed 140 eye procedures done on a total of 127 patients, with iERM, at the Beth Israel Deaconess Medical center in Boston, Massachusetts between the years of 1998 and 2015. Since iERM is a disease of exclusion, any patient with history of previous retinal surgery (cataract extraction with posterior intraocular lens placement was not excluded) or any other retinal diseases associated with the development of ERM were excluded. The appropriate candidates were divided by the procedures that were performed. The patients were separated into two major groups. The first were patients that had ERM only membrane peel while the other were patients that had ERM and ILM membrane peeling during the surgeries. Aside from preoperative and postoperative visual acuities, other information including lens status (phakic, aphakic, pseudophakic) preoperatively and postoperative, type (kenalog with or without ICG) and duration (0.5min, 1 min, 1.5 min) of the stains used, any prior or successive surgeries were collected for analysis.

Logarithm of the Minimum Angle of Resolution (LogMAR)

In order to compare the various postoperative and preoperative visual acuities, the logMAR scores were used (Holladay, 1997). The visual acuities were converted from Foot scale into the LogMAR score via the following equation.

LogMAR= - Log (20/Distance of the best line read in feet)
The conversion chart below was used.

Table 1: Conversion table between vision in feet scale to LogMAR score.

<table>
<thead>
<tr>
<th>Visual Acuity (Feet)</th>
<th>LogMAR</th>
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<tbody>
<tr>
<td>Hand motion (HM) 20/20000</td>
<td>3.0000</td>
</tr>
<tr>
<td>Count Fingers (CF) 20/2000</td>
<td>2.0000</td>
</tr>
<tr>
<td>20/400</td>
<td>1.3010</td>
</tr>
<tr>
<td>20/200</td>
<td>1.0000</td>
</tr>
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Diagnosis

Before undertaking any surgical interventions, a complete dilated ophthalmoscopic examination along with and OCT study were performed to ensure the appropriate diagnosis. Once the diagnosis was confirmed, the patient was provided information on ERM including its origin, progression, treatment options, its potential recurrence, and prognosis. While discussing treatment options the physician would weigh the pros and cons of observation versus surgical treatment, PPV along with ERM peeling, to ensure the patients were fully informed.

Lastly, if the patients chose to follow through with a surgical treatment, they were informed that any intraocular procedures are associated with a 1 in
1,000 risk of bleeding and infection which can lead to total loss of vision. Any patient who undergoes retina surgery is at risk of developing retinal tears or retinal detachment in approximately 1 in 100 patients. This problem can typically corrected at the time of surgery or may need additional surgery. Also noted, that vitrectomy is also associated with postoperative cataract formation in most patients over the age of 50 years of age. Thus Phakic patients with early cataract formation were suggested to undergo simultaneous phacoemulsification and posterior intraocular lens placement to eliminate the need of potential postoperative resurgery. Once the patient was fully informed on their diagnosis, the treatment options, and potential risks, they signed consent forms and were scheduled for the next available surgery date.

**Surgical Procedure**

At the operating room, EKG, O2, and blood pressure monitors were placed and monitored throughout the case. The operative eye was prepped and draped in the usual ophthalmic fashion and a wire lid speculum was placed to keep the lid apart. A retrobulbar infusion of a 50:50 mixture of 2% lidocaine and 0.75% Marcaine with epinephrine was given behind the operative eye to produce suitable anesthesia and akinesia. Sclerotomies were made 3.5 mm posterior to the limbus in the superonasal, superotemporal, and inferotemporal quadrants. A 4 mm infusion cannula was inserted into the inferotemporal sclerotomy. The tip of
the infusion cannula was inspected to ensure that it was in the vitreous cavity prior to turning on infusion.

At this point if a phacoemulsification and posterior intraocular lens implantation were planned, they would be performed. Then, the light pipe and vitreous cutter were used to perform a complete central and peripheral vitrectomy. Kenalog (triamcinolone acetonide) was used to stain the vitreous. If the patient still had a fully- or partially- attached posterior hyaloid, the vitreous cutter and light pipe were then used to perform a complete central and peripheral vitrectomy. Once a complete vitrectomy was achieved, attention was paid to the macula. More kenalog was injected to stain the ERM. ILM forceps were used to peel the ERM. Once this was achieved, then if ILM peeling was intended, then ICG dye was used to stain at varying durations depending on the surgeon’s preference. If the staining was not sufficient, restaining was attempted. Once sufficient staining was achieved, the ILM was peeled.

Once completed, a 360-degree scleral depressed examination was performed, and the surgeon would search for any evidence of retinal tears or detachments. Subsequently, if none were found, the sclerotomies were closed and ensured to be water-tight. The pressure in the eyes were checked at the conclusion of the case. A subconjunctival injection of Kefzol and dexamethasone were given. The Operative eye was patched with 1 drop of scopolamine 0.25%, bacitracin ointment, a soft eye pad and a hard eye shield. The patient was taken to the recovery room.
Statistical analysis

Statistical analysis were performed through a two-tailed student T-test to compare different groups. Statistical analysis were accepted as significant with a p value of <0.05. Data are presented as means ± SEM.
RESULTS

ERM Surgery

We first began our analysis by compiling the data together to see whether the both ERM surgeries are able to significantly improve vision postoperatively. We found that when comparing the preoperative visual acuity to the postoperative visual acuity, the visual acuity (expressed as a logMAR score) had significantly improved (p<0.0001) from an average of 0.6147 ± 0.0314 preoperatively to 0.3340 ± 0.0270 (Figure 10).

Figure 10: Overall Efficacy of ERM surgery. Preoperative and postoperative visual acuities, converted into LogMAR score, of all patients undergoing surgical treatment for iERM. Data presented as mean ± or – SEM; n=140 for the total number of eyes that underwent ERM surgery.
Consequently, we wanted to analyzed the preoperative and postoperative mean logMAR score of patients that underwent ERM only peeling and compare to patients that had ERM and ILM membrane peeling. Patients in the ERM only group, showed a significant (P<0.0006) improvement from 0.6028 ± 0.0422 to 0.3814 ± 0.0466. Similarly, the ERM and ILM peeling group showed a similar trend with the mean preoperative logMAR score of 0.6267 ± 0.0469 significantly (P<0.0001) improving to 0.2867 ± 0.0264 postoperatively (Figure 11).

Figure 11: Outcome of ERM surgery categorized by protocol. Preoperative and post operative visual acuities, converted into LogMAR score, of patients undergoing surgical treatment for iERM divided into two groups: ERM-Only peel and Combine (ERM + ILM) Peel. Data presented as mean + or – SEM; n=70 for ERM-only group; n=70 for Combined peel group. Brackets above the bars depict statistical significance between the two bars.
We then wanted to further explore the surgical outcomes of the two surgical protocols. In turn, we compared the average change of visual acuity between the two groups (ERM only versus ERM and ILM) after undergoing surgical intervention. The ERM and ILM peel group demonstrated an improvement by $0.3400 \pm 0.0369$. In contrast, the ERM only group only showed a $0.2213 \pm 0.0462$ mean change in logMAR score. The difference between the two mean changes in logMAR score is statistically significant ($P<0.0467$) (figure 12).

**Figure 12: Comparing the outcome of different ERM surgery protocols.** Mean change in visual acuity, in LogMAR score, of patients undergoing surgical treatment for iERM divided into two groups: ERM-Only peel and Combine (ERM + ILM) Peel. Data presented as mean + or – SEM; n=70 for ERM-only group; n=70 for Combined peel group.
**Cataract surgery**

Since, both ERM surgeries were often but not always accompanied with phacoemulsification and posterior intraocular lens placement, we wanted to analyze the possible effect of cataract surgery and potential difference in prognosis. Consequently, we compared the mean change in LogMAR score between three groups: patients that had simultaneous cataract surgery, phakic patients with only the PPV without cataract surgery, and lastly, pseudophakic patients that had cataract surgery done prior to the PPV. The analysis of the data showed no statistically significant between the three groups (Figure 13).

![Mean Change in Visual Acuity](image)

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<th>Group</th>
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<tr>
<td>Simultaneous Cataract Surgery (Phakic)</td>
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<tr>
<td>Previous Cataract Surgery (Pseudophakic)</td>
<td>$0.2445 \pm 0.0551$</td>
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**Figure 13: Overall impact of lens status and cataract surgery on outcome of ERM surgery.** Mean change in visual acuity, in LogMAR score, of all patients
undergoing surgical treatment for iERM divided into three groups: No cataract surgery, Simultaneous Cataract Surgery, Previous Cataract Surgery. Data presented as mean + or – SEM; n=28 for No cataract surgery group; n=66 for Simultaneous cataract surgery group; n=46 for Previous Cataract Surgery group.

We then further explored the possible influence of cataract surgery on surgical outcome of ERM surgery by dividing the patients into ERM-only peel and ERM and ILM peel and further divided up by the cataract surgery status (Figure 14). Notably, no statistically significant difference was found within ERM-only peel or ERM and ILM peel subgroups. Interestingly, statistically significant difference was found between pseudophakic ERM-only peel patients and phakic combined (ERM and ILM) peel patients that underwent simultaneous cataract surgery (p<0.0185) showing a greater improvement in the latter group. Furthermore, a statistically significant difference was also found between pseudophakic ERM-only peel patients and pseudophakic combined (ERM and ILM) peel patients (p<0.0127) with the combined peel showing a greater improvement. It should be noted that of the all the categories a significant difference (P<0.0265) in postoperative visual acuity was found between pseudophakic ERM-only peel patients (0.4768 ± 0.0878) and phakic ERM and ILM peel patients that underwent simultaneous cataract surgery (0.2747 ± 0.0380). Aside from these two groups no significant difference in postoperative visual acuity were detected. (Figure 15)
Figure 14: Impact of lens status and cataract surgery on outcome of ERM surgery evaluated by groups. Mean change in visual acuity, in LogMAR score, of patients undergoing surgical treatment for iERM divided to ERM-only peel or Combined (ERM+ILM peel) were further categorized into three groups: Simultaneous Cataract Surgery, No cataract surgery, Previous Cataract Surgery. Data presented as mean + or – SEM; For the ERM-Only peel group n=34 for Simultaneous cataract surgery subgroup, n=11 for No cataract surgery subgroup, and n=25 for Previous Cataract Surgery subgroup. For the ERM+ILM peel group n=32 for Simultaneous cataract surgery subgroup, n=17 for No cataract surgery subgroup, and n=21 for Previous Cataract Surgery subgroup. Brackets above the bars depict statistical significance between the two bars.
Figure 15: Postoperative visual acuity divided by lens status, cataract surgery and surgical protocol. Mean Postoperative Visual Acuity, in LogMAR score, of patients undergoing surgical treatment for iERM divided to ERM-only peel or Combined (ERM+ILM peel) were further categorized into three groups: Simultaneous Cataract Surgery, No cataract surgery, Previous Cataract Surgery. Data presented as mean ± or – SEM; For the ERM-Only peel group n=34 for Simultaneous cataract surgery subgroup, n=11 for No cataract surgery subgroup, and n=25 for Previous Cataract Surgery subgroup. For the ERM+ILM peel group n=32 for Simultaneous cataract surgery subgroup, n=17 for No cataract surgery subgroup, and n=21 for Previous Cataract Surgery subgroup. Brackets above the bars depict statistical significance between the two bars.

ICG staining and duration

In an effort to explore the potential impact of the ILM staining via ICG stain and the potential impact that the duration of the stain used. We first compared procedures that utilized ICG and ones that did not. Procedures that did not utilize
ICG stain showed a mean change in LogMAR score of 0.2458 ± 0.0461 which did not show a statistically significant difference to procedures that utilized ICG stain presenting a mean change in LogMAR of 0.3136 ± 0.0382. Subsequently, we further investigated the procedures that utilized ICG stain by putting them into 3 groups based on duration. The three groups were 0.5 min, 1 min, and 1.5 min and presented mean change in visual acuity of 0.2172 ± 0.0773, 0.3293 ± 0.0471, and 0.3079 ± 0.2822, respectively. The differences between the three groups were not statistically significant. (Figure 16)

![Figure 16: Impact of ICG on outcome of ERM surgery](image)

**Figure 16: Impact of ICG on outcome of ERM surgery.** Mean change in visual acuity, in LogMAR score, of patients that utilized ICG compared to ones that did not. The group that used ICG was further divided by duration (0.5 min, 1.0 min, 1.5 min used. Data presented as mean + or – SEM; n=69 for Procedures done without ICG; n=71 for procedures that utilized ICG; n=8 for 0.5 min group; n=53 for 1.0 min group; n=10 for 1.5 min group.)
Reoperation

The patients' records were also analyzed for any records of reoperation for recurrent ERM or any other retinal conditions, as well as phakic patients receiving cataract surgery after their ERM surgery. Out of the 70 ERM-only procedures that were done, 16 (22.9%) required a successive retinal operation. Out of the 16 successive operations, 10 (14.3%) were for recurrent ERM while 6 (8.57%) were associated with other retinal conditions. On the other hand, out of the 70 ERM and ILM peel procedures that were performed, only 2 (2.86%) needed a successive reoperation; one (1.43%) for a recurrent ERM while the other (1.43%) was for another retinal condition. It is also noteworthy to add that out of 28 phakic patients (11 ERM-Only peel, 17 ERM and ILM peel) that underwent ERM surgery, 11 (39.2%) developed cataracts and returned for phacoemulsification and posterior intraocular lens placement.
DISCUSSION

To date, the benefit of surgical intervention in improving vision in patients with ERM has been shown (Bu et al., 2014; Folk et al., 2015). However, the literature has not explicitly examined patients with iERM and the potential outcome of surgical intervention utilizing the potential benefits of a combined peel procedure. In this study, we have first demonstrated the overall efficacy of surgical intervention in treating iERM. The data suggest an overall significant improvement logMAR score postoperatively. This trend was also demonstrated when the surgical interventions were divided by protocol (ERM-only peel and ERM and ILM peel). Of interest is the analysis on the extent of improvement when comparing these two categories. The literature has yet to achieve consensus on whether removal of ILM significantly enhances the surgical outcome when treating ERM. The analysis of our data showed a statistically significant difference between the postoperative changes observed within each group suggesting that ERM peel along with ILM peel may be the more appropriate option since it exhibited the more significant improvement.

In addition, when comparing recurrence or reoperation on the same eye, our data illustrated a significant difference between the two groups by ILM peel patients showing significantly smaller recurrence and reoperation. These finding are consistent with the belief of the potential contribution of the ILM in the pathogenesis of iERM and its recurrence. Since the ILM is the basement membrane of the retina, it possesses the properties to provide a more favorable
and proliferative environment for tissue formation (Lois et al., 2011; Semeraro et al., 2015; Ternent et al., 2012).

We hypothesize that the removal of ILM ensures a better outcome due to two reasons. The first is due to its advantageous position during the surgery. Because, the ILM is a deeper tissue relative to the ERM during a PPV, its removal can help ensure the removal of the superficial ERM in its entirety. This is important since any portions of the ERM left within the eye after the procedure, increases the likelihood of its proliferation and recurrence. Secondly, the removal of the ILM will also eliminate the favorable proliferative environment that may nourish any remaining segments ERM. Thus, taking these factors into account, one will seemingly favor the removal of ILM along with ERM during the procedure. Within its capacity, this study has not only demonstrated the efficacy of surgical intervention in treating ERM, but has also demonstrated that a more favorable outcome may be achieved when ILM is also removed.

Our investigation helped shed some light on potential standards that may be incorporated into the surgical protocol. As mentioned earlier, PPV surgeries in phakic patients has shown to lead a slow progression to developing cataracts and as a result PPV surgeries on phakic patient is often recommended to be accompanied by phacoemulsification and Posterior intraocular lens placement (Chuang et al., 2012; Lee et al., 2011; Moisseiev et al., 2012; Yiu et al., 2013). This was consistent with our data as 39.2% of phakic patients that did not undergo simultaneous cataract surgery, needed a second operation to address
the newly developing cataracts. Furthermore, our data did not show any difference in the postoperative changes in visual acuities between patients that underwent simultaneous cataract surgery, no cataract surgery or had a previous cataract surgery. No significant difference was also seen when the patients were further divided by their ERM surgical protocol (ERM-Only peeling versus ERM and ILM peeling).

Interestingly, phakic ERM and ILM peel patients that underwent simultaneous cataract surgery showed a greater improvement in visual acuity compared to pseudophakic ERM-only peel patients. This is likely due to the additional visual improvement due to the cataract surgery supplementing the ERM surgery. In addition, pseudophakic ERM and ILM peel patients demonstrated a greater improvement in vision when compared to pseudophakic ERM-only peel patients. This may also act as further evidence to the ongoing discussion of combined peeling but signifying a greater improvement when both ERM and ILM are peeled. In turn, coupled with its lack of impact on ERM progression or recurrence, it seems that simultaneous cataract surgery along with PPV and ERM and ILM peel is a safe, effective, and cost efficient treatment plan in treating iERM.

In addition to examining the potential impact of simultaneous cataract surgery, we also explored the potential impact of the use of ILM dyes, more specifically ICG stain, on the outcome of surgical treatment. The use of the ILM stains ensures a more accurate and precise membrane peel however, with the
discovery of new ILM dyes, a question of potential toxicity and impact on the outcome of the surgery have been raised. The literature has raised questions on the safety of the use of ILM stains during ERM surgery and their potential impact on the outcome of the procedure. In this study, we found that the use of ILM stain, more specifically ICG, did not have an impact on the mean change in visual acuity postoperatively. Consequently, we have also taken a step further by analyzing the potential impact of the duration of the staining process. Our data did not show difference between the 3 groups (0.5 min, 1.0 min, 1.5 min) validating that the use of ICG dye is safe during the surgery. However future studies should examine the impact of other common ILM stains such as trypan blue and Brilliant Blue G.

A limitation of this current investigation is the number of subject used. Use of more patients with diagnosed iERM, would have helped us establish a stronger statistical relationship between the various groups. However, it is noteworthy to add that while selecting patients for iERM caution should be taken. This is important due to the fact the iERM is a diagnosis of exclusion meaning that once all the possible factors that may cause ERM are eliminated, the diagnosis of iERM may be confirmed. It is therefore important to have an accurate history of patients’ retinal condition and any intraocular surgery as they may cause the formation of secondary ERM. Since the data presented in this study have been taken from a period of time spanning over 17 years, and information collection and technology have changed over the years, some
patients may have been misidentified with iERM instead of secondary ERM despite the investigator’s comprehensive study of all patient history. In addition, the data presented, are treatments done by one surgeon which may be a potential confounding variable. Consequently, we suggest the collaboration of various physicians to compile a much larger database to not only increase the number of participants but to also eliminate this potential confounding variable.

To further strengthen the results, we propose that future studies should also obtain data on the Central Foveal Thickness (CFT). As mentioned earlier, CFT is a clinical measurement that could assess the success of the surgery postoperatively (Folk et al., 2015). Due to our limited access to the earlier data, we were not able to assess the relationship between the ERM-only peel group and the combined peel group. Based on the results from the current investigation, we hypothesize that a significant change in CFT would be observed between the two groups and is worthy of further investigation. Lastly, with the emergence of new technologies and techniques to study the eye particularly with the MRI, a future investigation can examine the choroidal blood flow through MRI in patients with iERM (Maleki, Dai, & Alsop, 2011). The investigation may further this proposal by examining preoperative and postoperative choroidal blood flow of patients that undergo surgery to treat ERM. This study may in fact provide better insight into the idiopathic pathogenesis of this condition.
In closing, in this study we were able to demonstrate the efficacy of surgery in treating iERM. We then further demonstrated greater benefit of combined (ERM and ILM) peeling during the surgical intervention. Subsequently, the most effective and cost efficient surgical intervention was found to be combined cataract and membrane peeling due to its significant postoperative vision improvement and elimination of the need for a second operation. Lastly, the use of ICG stain is recommended as it is not toxic and will help the surgeon better visualize the various structures during the procedure. We hope that future studies shed light on the pathogenesis of procedure since its prevention may be more cost-effective and less invasive.
REFERENCES


CURRICULUM VITAE

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EDUCATION

Boston University School of Medicine – Boston, MA
Masters of Science in Medical Sciences, 2016 (Anticipated)
GPA: 4.00

Ryerson University – Toronto, Canada
Post-baccalaureate (Non-degree), 2013-2014
GPA: 4.00

University of Toronto – Toronto, Canada
Honors Bachelors of Science with High Distinction, June 2013
GPA: 3.67
• Double major in cell and molecular biology and human biology: health and
disease

RESEARCH EXPERIENCES

2015-Current  Dr. Jorge G. Arroyo, Department of Ophthalmology
Beth Israel Deaconess Medical Center
• Clinical Assistant: tasked with performing
full eye examination along with OCT scans.
Also responsible to assist in various laser
and injection procedure
• Research Associate: assigned a number of
projects to pursue. A project evaluating
outcome of various surgical protocols
completed for thesis requirement of the
masters program. 2 abstracts that were
accepted to ARVO conference in MAY
2016.
2012-2013  Dr. Tony Lam, Department of Physiology, University of Toronto

- Research student for undergraduate thesis project
- Trained in standard lab safety, animal handling, anesthesia, radioactive training, and surgical procedures (brain and vascular)

Publication:

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**OTHER EXPERIENCES**

2015-Current  Boston University Tutor

- Tutor for Dental physiology and Biochemistry courses
- Tutor for Medical School equivalent physiology and Biochemistry courses

2012  Lab Volunteer at Dr. Lam’s Diabetes Research Laboratory

- Preparing supplies such as making the lines for the surgeries and experiments, preparing tubes, labeling tubes/vials and other supplies that trainees use for their projects
- Organizing samples for the lab trainees

2011-2013  Co-founder of Friends of Sick Kids Organization

  **Co-Vice president (2012-2013)**

- Responsible for the general supervision and organization of the club
- Maintain consistent communication within the club and with its affiliates, including answering email inquires that cannot be answered by the awareness director

  **Communication Director (2011-2012)**

- Responsible for the website and all other social media
- Planning and transcribing general meetings and managing all organization communications

**2011-2013**  
**Toronto General Hospital (TGH) Volunteer**
- Provide assistance at the Surgical Admission Unit
- Create patient files and charts
- Assist patients to the waiting area
- Running errands for staff
- Ensuring patients’ questions and concerns are relayed to the appropriate staff
- Performing ancillary duties to assist staff

**2011**  
**St. Michaels Hospital**
- Shadowed Dr. R. Loch Macdonald (Neurosurgeon)

**2011**  
**Cancer Society Daffodil Days Campaign Volunteer**
- Sold daffodil flowers and daffodil pins to help raise funds and awareness towards cancer

**2010-2013**  
**St. Michael’s College Residence Council Vice President and Council Member**
- Responsible in organizing and planning sporting and social event for fellow residents
- Member of Double Blue Crew responsible with helping out with general residence needs

**AWARDS**

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OTHER ACTIVITIES

• Member of University of Toronto intramural sports teams for St. Michael's College indoor/outdoor soccer (2009-2013)
• Captain/Coach of the Hanger Competitive indoor soccer team (2009-2014)

SKILLS

• Fluent in both English and Farsi (Reading, Writing, Speaking)
• Competent user of both Macintosh and Windows computers along with Microsoft office (word, powerpoint, and excel)