



## Is Cystoid Macular Edema More Frequent In Vitrectomized Internal Limiting Membrane-Peeled Eyes Undergoing Phacoemulsification?

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### Authors' contributions

This work was carried out in collaboration among all authors. Author HZ designed the study and wrote the protocol. Authors HL and ID did the literature search, collected all data, performed the statistical analysis, and wrote the manuscript. Author HZ edited the manuscript. All authors read and approved the final manuscript.

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Short Communication

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### ABSTRACT

**Purpose/Aim of study:** We postulate that the timing of phacoemulsification relative to pars plana vitrectomy, internal limiting membrane peel (before, during or after) and gas is an important risk factor for cystoid macular edema.

**Materials and Methods:** We report a retrospective study of 43 eyes in 43 patients. All patients underwent vitrectomy, internal limiting membrane peeling and gas for full-thickness macular hole. Patients were categorized according to their phakic status prior to vitrectomy. Group 1 remained phakic through the 12-month study and acted as a control group, group 2 had combined surgery, group 3 were pseudophakic prior to vitrectomy and group 4 became pseudophakic subsequent to vitrectomy. Patients with postoperative optical coherence tomography (OCT)-proven CME with at

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least one cyst within the OCT field associated with increased central macular thickness (CMT) were identified.

**Results:** CME was noted in 6/43 patients (14%). CME occurred in 38% of group 4 compared to 0% of group 1, 11% of group 2 and 11% of group 3. This difference did not reach statistical significance when rates were compared to group 1 (Anova: group 2:  $p = 0.853$ ; group 3:  $p = 0.876$ ; group 4:  $p = 0.173$ ). The mean ( $\pm$  standard deviation) LogMAR best-corrected mean visual acuity (BCVA) improved from 0.44 ( $\pm 0.27$ ) at time of CME diagnosis to 0.35 ( $\pm 0.19$ ), with a mean decrease in CMT from 392.2 ( $\pm 102.5$ )  $\mu\text{m}$  to 287.7 ( $\pm 34.0$ )  $\mu\text{m}$ .

**Conclusions:** We report a trend of higher incidence and recurrence of CME in vitrectomized ILM-peeled eyes undergoing phacoemulsification than in other sequences of these procedures.

*Keywords: Cystoid macular edema; full-thickness macular hole; vitrectomy; phacoemulsification; optical coherence tomography; internal limiting membrane.*

## 1. INTRODUCTION

Post-operative cystoid macular edema (CME) is difficult to predict and a source of morbidity to patients affected. CME may be classed as CME affecting vision (symptomatic CME) or CME detected by optical coherence tomography (OCT-evident CME). The reported incidence of symptomatic CME post routine phacoemulsification (PE) is relatively low (0.1 to 2.35%), but OCT-evident CME is considerably higher at 4 to 11% [1]. Risk factors related to PE that predispose eyes to CME include factors at the time of surgery including vitreous loss, vitreous traction at incision sites, vitrectomy for retained lens fragments, iris trauma, posterior capsule rupture, intraocular lens (IOL) dislocation, early postoperative capsulotomy, and the use of iris-fixated or anterior chamber IOLs [2,3]. Eyes with diabetic maculopathy,[4,5] previous uveitis [6] retinal vein occlusion (RVO), epiretinal membrane, and prostaglandin analogs use are all associated with a higher risk of developing CME following PE [7].

The incidence of CME would seem to be higher for posterior segment procedures. In a series of pars plana vitrectomies (PPV) for floaters the rate reported is 5.5%, in patients with no ocular comorbidities, although the type of CME is not specified [8]. An OCT-evident CME rate of 26% was reported in patients who underwent PE in eyes that had previous PPV and internal limiting membrane (ILM) peel for full thickness macular hole (FTMH) versus 0% CME in control cases who underwent PE alone [9]. This rate appears much higher than a reported symptomatic CME rate for simultaneous PE and PPV (phacovitrectomy) of 1.9% [10] to 8.1% [11].

We postulated that the timing of PE relative to PPV (before, during or after) is an important risk

factor for CME. We aim to report the rates of OCT-evident and symptomatic CME in patients undergoing PPV preceded by, followed by and concurrent with PE.

## 2. MATERIALS AND METHODS

We report a retrospective study of 43 eyes in 43 patients who underwent PPV and ILM peeling and gas for FTMH (stage 3 or 4) at the Vitreoretinal service of Barts Health NHS Trust, London, UK. All patients with retinal vascular occlusions, diabetes and previous uveitis were excluded. Patients underwent 20 gauge ( $n = 11$ ) or 23 gauge ( $n = 32$ ) PPV. All procedures were performed by a single surgeon (HJZ). All adults who underwent PPV ILM peel for FTMH between 2008 and 2012 inclusively, with one year of follow up, were included. All patients received dexamethasone (0.1%) topical regime four times per day in the operated eye after every procedure for one month. Patients did not routinely receive prophylactic topical non-steroidal anti-inflammatories (NSAIDs) post-operatively. Patients with CME had at least one cyst within the OCT field on the macular cube 512x128 scan, associated with increased central macular thickness (CMT  $> 250\mu\text{m}$  was taken as increased[12]) on spectral domain OCT (Cirrus HD-OCT, Carl Zeiss Meditec, Dublin, CA, USA). All patients had OCT scans at 1, 3, 6, 9 and 12 months post PPV or PE. The group of 8 patients who were phakic and had PPV/ILM peel for FTMH (group 1) acted as a control group as they did not undergo PE at any stage. Group 2 patients had concurrent PE and PPV/ILM peel for FTMH. The group 3 patients had already undergone PE at other practices before presenting to our service with FTMH, the data from their first procedure is limited. Group 4 underwent PPV/ILM peel for FTMH under our care and we performed their subsequent PE.

Ethical approval was not required, given that the study was retrospective and all treatment was administered as per the standard of care. This study observed the tenets of the Declaration of Helsinki.

Statistical analysis was performed using Aabel 3 statistical package (Gigawiz Ltd. Co, Oklahoma, USA). A p value of <0.05 was taken as statistically significant.

### 3. RESULTS

The mean age of the 43 patients in this study was 68.1±12.7 years, in which 67% of them were female. The mean stage of FTMH was 3.0±0.6. OCT-evident CME occurred in 38% of group 4 compared to 0% of group 1, 11% of group 2 and 11% of group 3. This difference did not reach statistical significance when rates were compared to group 1 (Table 1; Anova: group 2 p = 0.853; group 3: p = 0.876; group 4: p = 0.173).

The mean (± standard deviation; SD) LogMAR best-corrected mean visual acuity (BCVA) for all patients improved significantly from 0.85 ± 0.37 to 0.49±0.37 at 12 months postoperatively (student's t-test: p = 0.001, Fig. 1). The study eye was a right eye in 20/43 (47%) of cases. The FTMH was closed with a single procedure in 42/43 patients (98%). The remaining case resolved with a second procedure. Group 4 had

a mean 12.3 (±11.1) months interval between procedures. The interval between procedures is not known for group 3, as their first procedures were performed in other units and the exact details were unavailable. The OCT findings of a typical case are depicted in Fig. 2.

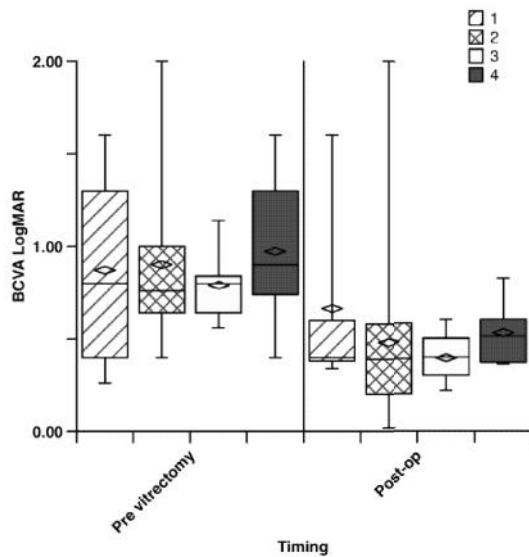
CME was noted in 6/43 patients (14%, Table 1), between 1 and 5 months post op (mean 3.3 months). Four cases were symptomatic and two were asymptomatic, but one of these patients became symptomatic when the CME recurred. All CME resolved with 6 weeks of topical NSAIDs (Ketorolac) and topical steroids (dexamethasone 0.1%), followed by a tapering period. Three patients developed symptomatic recurrent CME between 9 and 12 months postoperatively, which resolved with further topical NSAIDs and steroids. Two of these patients had PPV ILM-peel followed by PE (Group 4), the remaining patient had PE followed by PPV ILM-peel (Group 3).

For CME patients, the mean (± SD) LogMAR BCVA improved from 0.44 (±0.27) at time of CME diagnosis to 0.35 (±0.19) following treatment, with a mean decrease in CMT (± SD) from 392.2 (±102.5) µm preoperatively to 287.7 (±34.0) µm at 12 months. The final mean BCVA and CMT of CME and non-CME patients are depicted in Figs. 3A and 3B, respectively (Anova: P = 0.587 and 0.389, respectively).

**Table 1. Breakdown of cystoid macular edema by sequence of surgery and manner of edema**

Procedure	OCT-evident CME	CME Sympt	Late recurrence	P value
Group 1: PPV ILM-peel (phakic, control) n =8	0 (0%)	0 (0%)	0 (0%)	
Group 2: Combined (PE +PPV ILM-peel) Group 2, n =18	2 (11%)	1 (6%)	0 (0%)	0.853
Group 3: PE 1 <sup>st</sup> then PPV ILM-peel, n = 9	1 (11%)	1 (11%)	1 (11%)	0.876
Group 4: PPV ILM-peel 1 <sup>st</sup> then PE, n = 8	3 (38%)	2 (25%)	2 (25%)	0.173

*Summary of patients undergoing each procedure by number of cases of cystoid macular edema (CME). Total: The number of cases undergoing each procedure; OCT-evident CME: The number (and percentage) of cases with acute postoperative CME evident on ocular coherence tomography (OCT); CME Sympt: The number (and percentage) of cases who developed acute symptomatic postoperative CME; Late recurrence: The number number (and percentage) of cases who developed recurrent postoperative CME (all of which were symptomatic); PPV ILM-peel (phakic): Eyes that underwent pars plana vitrectomy (PPV) and internal limiting membrane (ILM) peel; Combined (PE +PPV ILM-peel): Eyes that underwent simultaneous phacoemulsification (PE) with PPV and ILM-peel; Sequential 1 (PE 1<sup>st</sup> then PPV ILM-peel): Eyes that underwent PE and then subsequently underwent PPV and ILM-peel; Sequential 2 (PPV ILM-peel 1<sup>st</sup> then PE): Eyes that underwent PPV and ILM-peel and subsequently underwent PE. P value. Result of ANOVA comparison between OCT-evident CME rates for, Groups 2, 3 and 4 compared to group 1 (control). P<0.05 was taken as statistically significant*



**Fig. 1. Best-corrected visual acuity pre and post-operatively**

Box-Whisker plot depicting LogMAR best-corrected visual acuity (BCVA) of all 4 groups prior to pars plana vitrectomy and ILM peeling for full-thickness macular hole (pre vitrectomy) and 12 months (post-op) following the last procedure. Pre- and postoperative refers to their most recent procedure, albeit phacoemulsification, pars plana vitrectomy or combined phacovitrectomy. Group 1 remained phakic throughout and acted as a control group, group 2 had combined surgery, group 3 were pseudophakic prior to vitrectomy and group 4 became pseudophakic subsequent to vitrectomy. Bar in box represents median value, diamond represents mean values, and the whiskers depict the 5<sup>th</sup> and 95<sup>th</sup> percentiles

#### 4. DISCUSSION

Our rates of symptomatic CME in the combined group (Group 2) is comparable to that previously reported (1.9%<sup>4</sup> [10] to 8.1%<sup>5</sup> [11] compared to 9% in this study), which suggests the rate of OCT-evident CME in our sample may approximate that in the wider population. The incidence of CME was highest in group 4 relative to all the other groups, recurrent CME was also higher in this group. While our results did not reach statistical significance so that this trend warrants reporting, it is noteworthy that CME was observed more frequently if PE followed PPV than the reverse. A rate of 26.3% (5 of 19) OCT-evident CME was reported in eyes that underwent PE subsequent to PPV/ILM peel (analogous to our group 4), [9] the rate of 38% in our study, while somewhat higher confirms the finding of Mylonas et al. [9]. We were concerned

about the effect of timing, of PE relative to PPV/ILM peel surgery on CME, so we included patients who remained phakic during the study period as a control group, and we looked at the incidence of CME if PE was performed prior to, with or subsequent to PPV/ILM peel for FTMH.

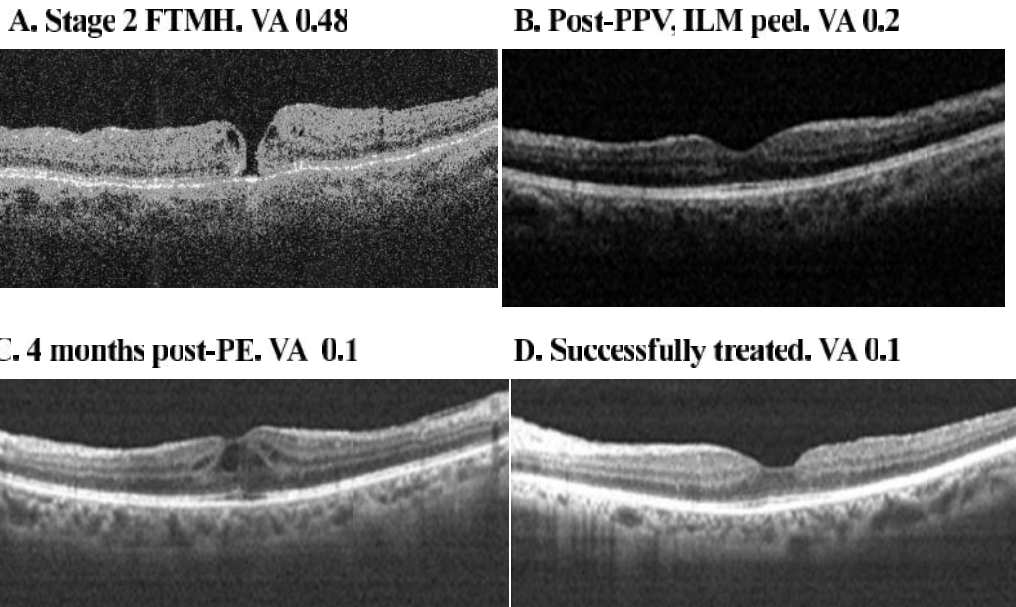
The interstitial pathway from the vitreous cavity to the subretinal space is formed by the external and internal limiting membranes. The junctions of the external limiting membrane (ELM) are not sealed and, consequently, can only partially limit the movement of large molecules. However, the ILM has no significant influence on water movement [13]. Thus, the balance between static and dynamic vitreous tractional forces determines whether CME forms a macular hole or becomes chronic.

Whilst ILM peeling may have beneficial effects on CME because it removes tangential traction, increases retinal oxygenation, reduces vascular endothelial growth factor (VEGF) production, and allows intraretinal fluid from the macula to reach the vitreous cavity, it also alters the inner retinal structure possibly resulting in greater responsiveness to inflammatory stimuli [13]. The beneficial effect of ILM peeling may therefore be lost in the setting of inflammation post PE, with increased risk of CME.

It is possible that minute nuclear lenticular material may enter the vitreous cavity during uncomplicated PE via minute zonular gaps, and this material may have greater inflammatory potential in vitrectomized eyes than eyes where it is subsequently removed with the vitreous.

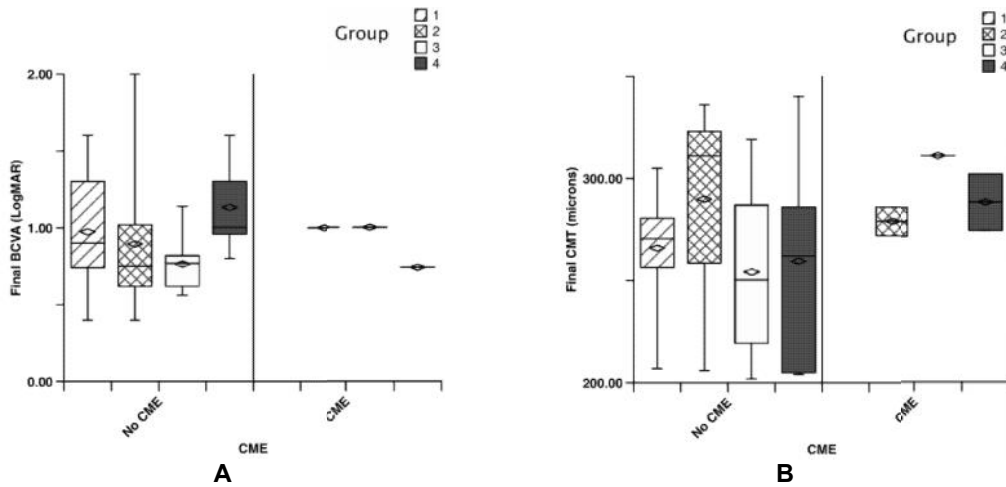
The evidence that prophylactic topical NSAID regime reduces CME post PE is not easy to interpret due to other factors such as concurrent topical steroid use [14]. Whilst NSAIDs are routinely used to treat CME, it is postulated that intraocular inflammation drives CME formation and that NSAIDs better penetrate the blood ocular barrier than topical steroids, so may be more effective in CME [14].

To our knowledge, this is the first study that compares the rate of CME in both sequences of PE before or after PPV/ILM peel, with patients who had combined surgery and those who had PPV/ILM peel without PE (Table 1).



**Fig. 2. Case study serial OCT analysis of a single eye**

A. Optical coherence tomography (OCT) scan, left macula of a 61-year-old female with reduced vision and metamorphopsia of 3 weeks duration, showing a grade 4 full-thickness macular hole (FTMH). LogMAR best-corrected visual acuity (VA) of 0.48. This patient is from group 4, B. OCT scans of same eye 3 months post FTMH hole repair with pars plana vitrectomy and internal limiting membrane peel (PPV, ILM peel), showing a closed macular hole, C. OCT scan of same eye, 4 months post phacoemulsification (PE) demonstrating cystoid macular edema (CME), D. OCT scan of same eye 6 months post PE, after topical treatment with topical non-steroidal anti-inflammatories and topical steroids, showing resolution of CME



**Fig. 3. Best-corrected visual acuity and central macular thickness, in patients with cystoid macular edema versus those without macular edema**

Box-Whisker plot depicting A. final (12 month postoperative) LogMAR best-corrected visual acuity (BCVA) and B. final central macular thickness (CMT in  $\mu\text{m}$ ) of 4 groups, based on development of post-operative CME. Postoperative refers to their most recent procedure, albeit phacoemulsification, pars plana vitrectomy or combined phacovitrectomy. Group 1 remained phakic throughout and acted as a control group, group 2 had combined surgery, group 3 were pseudophakic prior to vitrectomy and group 4 became pseudophakic subsequent to vitrectomy. Bar in box represents median value, diamond represents mean values, and the whiskers depict the 5<sup>th</sup> and 95<sup>th</sup> percentiles

Our study is limited by sample size and retrospective design. The present data however, justifies a large prospective randomized trial to elucidate the relative risk of CME in relation to the timing of phacoemulsification in patients undergoing macular hole surgery. The lack of perioperative data relating to the PE procedures of the group 3 patients limits our ability to assess their macular appearance pre and post PE. It is possible that CME could have developed post PE and contributed to the FTMH formation, but was no longer present when the patient presented to our care.

Further work should include a study to evaluate the effects of prophylactic NSAIDs on the incidence of CME following macular hole repair and PE.

## 5. CONCLUSION

In conclusion, we report a trend towards a higher incidence of CME in vitrectomized ILM-peeled eyes when PE is performed subsequently, than other sequences with PE.

## CONSENT

All authors declare that 'written informed consent was obtained from the patient for publication of this case report and accompanying images.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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