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Journal Name:	Journal of Advances in Medical and Pharmaceutical Sciences
Manuscript Number:	2014_JAMPS_12865
Title of the Manuscript:	Is Cystoid Macular Edema More Frequent In Vitrectomized Internal Limiting Membrane-peeled Eyes Undergoing Phacoemulsification?
Type of the Article	Short communication

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound.

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PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Compulsory REVISION comments	Article is regarding retrospective study done (place and hospital/Institution not mentioned) to find out timing of phacoemulsification performed before, during and after PPV with ILM peeling for 43 eyes with full thickness macular holes. Authors describe the incidence of cystoids macular oedema in vitrectomized eyes. There are some difficulties in understanding the outcome of this retrospective study, nevertheless following are the reviewers comments that may help in revising the present study. Abstract 1. The procedure runs in three groups but in the results section there are four groups with phakic group inclusion. 2. The age group and the place and duration of the study is not mentioned in the methods and materials section.	Line 59 We report a retrospective study of 43 eyes in 43 patients who underwent PPV and ILM peeling for FTMH (stage 3 or 4) at the Vitreoretinal service of Barts Health NHS Trust, London, UK. Line 59 We report a retrospective study of 43 eyes in 43 patients. All patients underwent vitrectomy and internal limiting membrane peeling 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, group 2 had combined surgery, group 3 were pseudophakic prior to vitrectomy and group 4 became pseudophakic subsequent to vitrectomy. Line 82 The mean age of the 43 patients in this study was 68.1 ± 12.7 years. Line 59 We report a retrospective study of 43 eyes in 43 patients who underwent PPV and ILM peeling for FTMH (stage 3 or 4) at the Vitreoretinal



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	3. Results are once again confusing with inclusion of phakic group (4th group). Demographic details regarding age, sex and laterality of the disease process lacking. 4. Three patients had CME recurrence resolved with topical regime, but they say two patients had first PPV ILM peeling followed by PE and one patient had first PE followed by PPV ILM peeling. What was the rationale for considering these three patients for surgical intervention once CME resolved with topical medication? Introduction 1. Authors describe CME incidence in the introduction, can be enriched by inclusion of reference regarding how PE becomes a risk factor. What is the published incidence of CME for	service of Barts Health NHS Trust, London, UK. Line 65 All patients had OCT scans at 1, 3, 6, 9 and 12 months post PPV or PE. The mean age of the 43 patients in this study was 68.1 ± 12.7 years. The mean stage of FTMH was 3.0 ± 0.6. The FTMH was closed with a single procedure in 42/43 patients (98%). The remaining case resolved with a second procedure. Group 3 had a mean 12.3 (± 11.1) months interval between procedures. The interval between procedures is not known for group 4, 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 figure 1. CME occurred after the last procedure in all cases. No procedures were performed on patients with CME or history of CME. Line 37 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
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	FTMH without PE 2. There are three groups according the purpose of the study, but four groups with inclusion of phakic group. Why phakic group included (8) whether for control or comparison. (Line no. 47-50) Materials and methods Although the article is submitted under short communication category, authors should describe in detail regarding the methods followed which are insufficient in the present study. 1. Age, sex distribution and place of study with ethical clearance from the institution should be described with how patients were categorised. Is it from case sheets in patient/out patient records	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] Line 145 This is the first paper to our knowledge, to report an incidence for CME post PPV/ILM peel alone (Table 1). Line 72 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. Line 82 The mean age of the 43 patients in this study was 68.1 ± 12.7 years. The mean stage of FTMH was 3.0 ± 0.6. 67% of patients in this study were female. Line 60 at the Vitreoretinal service of Barts Health NHS Trust, London, UK. Line 78 Ethical approval was not required, given that the study was retrospective and all treatment was
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	2. What were the inclusion criteria? Is hypertension not included? 3. What were the indication for using PPV with 20 and 23 gauge 4. How long dexamethasone recommended 5. What was the method followed to measure the CMT and complete details of the instrument should be stated. (please include 1 or 2 images showing OCT of post PE CME 6. How many phakic/pseudophakic/cataract eyes-please make it clear	the standard of care. This study observed the tenets of the Declaration of Helsinki. Line 63 All adults who underwent PPV ILM peel for FTMH between 2008 and 2012 inclusively, with one year of follow up, were included. Hypertensive patients were included. This was during the period that the Trust switched from 20 to 23 gauge surgery. Line 65 All patients received dexamethasone (0.1%) topical regime four times per day in the operated eye after every procedure for one month Line 68 Patients with CME had at least one cyst within the OCT field on, macular 256 scan, associated with increased central macular thickness (CMT > 250µm was taken as increased[12]) on spectral domain OCT (Cirrus HD-OCT, Carl Zeiss Meditec, Dublin, CA, USA). Line 186 Figure 2. Case study Line 72 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
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	Results 1. Once again, results section is weak due to missing of age, sex and laterality of the disease process. Categorisation of the groups should be clear. 2. In the methods, they say topical dexamethasone used for all patients but here NSAIDs ketorolac included. Did they use both agents (Line no. 67-69)-please make it clear Discussion 1. should be drawn from the results obtained in this retrospective study	data from their first procedure is limited. Group 4 underwent PPV/ILM peel for FTMH under our care and we performed their subsequent PE. Line 163 Table 1. Line 83 The mean age of the 43 patients in this study was 68.1 ± 12.7 years. The mean stage of FTMH was 3.0 ± 0.6. 67% of patients in this study were female. Line 72 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. Line 67 Patients did not routinely receive prophylactic topical non-steroidal anti-inflammatories (NSAIDs) post-operatively. Line 108 Our rates of symptomatic CME in the combined group (group 2) is comparable to that previously reported ($1.9\%[10]^4$ to $8.1\%[11]^5$) compared to 6% in this study), which suggests our rate of OCT-evident CME approaches that in the
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	2. Describe how topical steroids/NSAI drugs help in CME resolution. 3. What factors are contributing to decreased incidence of CME in eyes underwent PE first?	population. The incidence of CME was highest group 4 relative to all the other groups, recurrent CME was also highest in this group. While our results did not reach statistical significance 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 under went 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. They included a group of PE patients as controls as they wished to report the rate of CME if PPV/ILM peel was performed in pseudophakic eyes,[9] we were concerned about the timing, so we included patients who remained phakic as a control group as they did not undergo PE at any stage, we looked at the incidence of CME if PE was performed prior to, with or subsequent to PPV/ILM peel for FTMH. Line 139 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.[15] 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.[15] Line 123 The interstitial pathway from the vitreous cavity
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	4. Discussion section needs improvement by inclusion of relevant references. Conclusion 1. How one can do PE in patients already underwent PPV ILM peeling without cataract formation (indications)	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 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.[14] 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 vitrectomised eyes than eyes where it is subsequently removed with the vitreous. We agree and have complied PE was performed if patients had symptomatic cataract.
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	2. Authors' advocated combined phacovitrectomy please explain (Line no. 99-100) References 1. Please improve with addition of relevant material	We have changed the conclusion Line 158 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. See references line 212
<u>Minor</u> REVISION comments	Although the paper needs major reorganisation of the protocol followed, authors attempted to find out the incidence of CME considering PE as a risk factor for 43 eyes before, during and after PPV ILM peeling for FTMH. A prospective study would be more validated than retrospective study	We recommend such a study. This work justifies such a project. Line 148 This limits our ability to extrapolate, however, this evidence justifies a large prospective randomized trial to elucidate the relative risk of the timing of phacoemulsification in such patients.
<u>Optional/General</u> comments	Authors may utilise the journal criteria for the text (2500-3500 words) and references (15-20) under short communication that will enrich the article.	We have increased the volume of text and number of references significantly