

Short Communication

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

Abstract

Purpose/Aim of study

We postulate that the timing of phacoemulsification relative to pars plana vitrectomy and internal limiting membrane peel (before, during or after) 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 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 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 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 (± 0.27) at time of CME diagnosis to 0.35 (± 0.19), with a mean decrease in CMT from 392.2 (± 102.5) μm to 287.7 (± 34.0) μm .

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.

31 Introduction

32

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

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

54 We postulated that the timing of PE relative to PPV (before, during or after) is an
55 important risk factor for CME. We aim to report the rates of OCT-evident and
56 symptomatic CME in patients undergoing PPV preceded by, followed by and
57 concurrent with PE.

58

59 Materials and Methods

60 We report a retrospective study of 43 eyes in 43 patients who underwent PPV and
61 ILM peeling for FTMH (stage 3 or 4) at the Vitreoretinal service of Barts Health NHS
62 Trust, London, UK. All patients with retinal vascular occlusions, diabetes and

63 previous uveitis were excluded. Patients underwent 20 gauge (n = 11) or 23 gauge (n
64 = 32) PPV. All procedures were performed by a single surgeon (HJZ). All adults who
65 underwent PPV ILM peel for FTMH between 2008 and 2012 inclusively, with one
66 year of follow up, were included. All patients received dexamethasone (0.1%) topical
67 regime four times per day in the operated eye after every procedure for one month.
68 Patients did not routinely receive prophylactic topical non-steroidal anti-
69 inflammatories (NSAIDs) post-operatively. Patients with CME had at least one cyst
70 within the OCT field on macular 256 scan, associated with increased central macular
71 thickness (CMT > 250µm was taken as increased[12]) on spectral domain OCT
72 (Cirrus HD-OCT, Carl Zeiss Meditec, Dublin, CA, USA). All patients had OCT scans
73 at 1, 3, 6, 9 and 12 months post PPV or PE. The group of 8 patients who were phakic
74 and had PPV/ILM peel for FTMH (group 1) acted as a control group as they did not
75 undergo PE at any stage. Group 2 patients had concurrent PE and PPV/ILM peel for
76 FTMH. The group 3 patients had already undergone PE at other practices before
77 presenting to our service with FTMH, the data from their first procedure is limited.
78 Group 4 underwent PPV/ILM peel for FTMH under our care and we performed their
79 subsequent PE.
80 Ethical approval was not required, given that the study was retrospective and all
81 treatment was the standard of care. This study observed the tenets of the Declaration
82 of Helsinki.

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

85 Results

86 The mean age of the 43 patients in this study was 68.1 ± 12.7 years, in which 67% of
87 them were female. The mean stage of FTMH was 3.0 ± 0.6 . OCT-evident CME
88 occurred in 38% of group 4 compared to 0% of group 1, 11% of group 2 and 11% of
89 group 3. This difference did not reach statistical significance when rates were
90 compared to group 1 (Table 1; Anova: group 2 p = 0.853; group 3: p = 0.876; group
91 4: p = 0.173).

92 The mean ($\pm$ standard deviation; SD) LogMAR best-corrected mean visual acuity
93 (BCVA) for all patients improved significantly from 0.85 ± 0.37 to 0.49 ± 0.37 at 12

94 months postoperatively (student's t-test: $p = 0.001$, Figure 1). The study eye was a
95 right eye in 20/43 (47%) of cases.

96 The FTMH was closed with a single procedure in 42/43 patients (98%). The
97 remaining case resolved with a second procedure. Group 3 had a mean 12.3 (± 11.1)
98 months interval between procedures. The interval between procedures is not known
99 for group 4, as their first procedures were performed in other units and the exact
100 details were unavailable. The OCT findings of a typical case are depicted in figure 2.

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

110 For CME patients, the mean ($\pm$ SD) LogMAR BCVA) improved from 0.44 ($\pm$ 0.27) at
111 time of CME diagnosis to 0.35 ($\pm$ 0.19) following treatment, with a mean decrease in
112 CMT ($\pm$ SD) from 392.2 ($\pm$ 102.5) μ m preoperatively to 287.7 ($\pm$ 34.0) μ m at 12
113 months. The final BCVA and CMT of CME and non-CME patients are depicted in
114 figure 3.

115

116 Discussion

117 Our rates of symptomatic CME in the combined group (group 2) is comparable to that
118 previously reported (1.9%[10]⁴ to 8.1%⁵[11] compared to 6% in this study), which
119 suggests the rate of OCT-evident CME in our sample may approximate that in the
120 wider population. The incidence of CME was highest in group 4 relative to all the
121 other groups, recurrent CME was also higher in this group. While our results did not
122 reach statistical significance so that this trend warrants reporting, it is noteworthy that
123 CME was observed more frequently if PE followed PPV than the reverse. A rate of
124 26.3% (5 of 19) OCT-evident CME was reported in eyes that underwent PE

125 subsequent to PPV/ILM peel (analogous to our group 4),[9] the rate of 38% in our
126 study, while somewhat higher confirms the finding of Mylonas et al. They included a
127 group of PE patients as controls as they wished to report the rate of CME if PPV/ILM
128 peel was performed in pseudophakic eyes,[9] we were concerned about the timing, so
129 we included patients who remained phakic as a control group as they did not undergo
130 PE at any stage, we looked at the incidence of CME if PE was performed prior to,
131 with or subsequent to PPV/ILM peel for FTMH.

132 The interstitial pathway from the vitreous cavity to the subretinal space is formed by
133 the external and internal limiting membranes. The junctions of the external limiting
134 membrane (ELM) are not sealed and, consequently, can only partially limit the
135 movement of large molecules. However, the ILM has no significant influence on
136 water movement.[13] Thus, the balance between static and dynamic vitreous
137 tractional forces determines whether CME forms a macular hole or becomes chronic.
138 Whilst ILM peeling may have beneficial effects on CME because it removes
139 tangential traction, increases retinal oxygenation, reduces vascular endothelial growth
140 factor (VEGF) production, and allows intraretinal fluid from the macula to reach the
141 vitreous cavity, it also alters the inner retinal structure possibly resulting in greater
142 responsiveness to inflammatory stimuli.[14] The beneficial effect of ILM peeling may
143 therefore be lost in the setting of inflammation post PE, with increased risk of CME.

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

148 The evidence that prophylactic topical NSAID regime reduces CME post PE is not
149 easy to interpret due to other factors such as concurrent topical steroid use.[15]
150 NSAIDs are routinely used to treat CME, it is postulated that intraocular
151 inflammation drives CME formation and that NSAIDS better penetrate the blood
152 ocular barrier than topical steroids, so may be more effective in CME.[15]

153 This is the first study that compares the rate of CME in both sequences of PE before
154 or after PPV/ILM peel with combined surgery and with patients who had PPV/ILM
155 peel without PE. This is the first paper to our knowledge, that reports an incidence for
156 CME post PPV/ILM peel alone (Table 1). Our study is limited by sample size and
157 retrospective design. This limits our ability to extrapolate, however, this evidence

158 justifies a large prospective randomized trial to elucidate the relative risk of the timing
159 of phacoemulsification in such patients. The lack of perioperative data relating to the
160 PE procedures of the group 4 patients limits our ability to assess their macular
161 appearance pre and post PE. It is possible that CME could have developed post PE
162 and contributed to the FTMH formation, but was no longer present when the patient
163 presented to our care.

164 Further work should include a study to evaluate the effects of prophalxtic NSAIDs on
165 CME incidence post macular hole repair with PE.

166

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

169

170

171

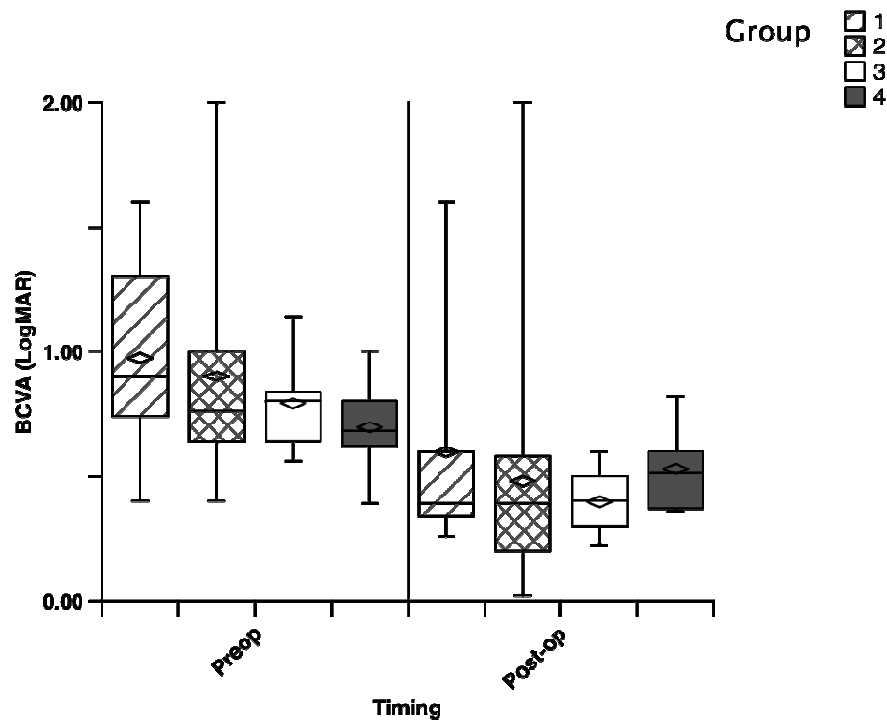
172

173 **Table 1.**

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

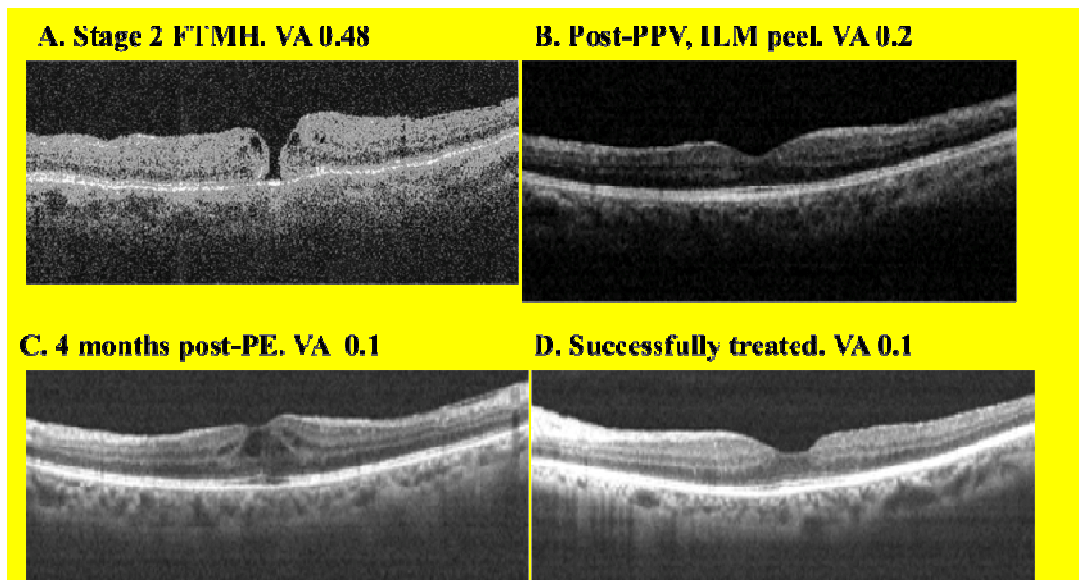
174 Summary of patients undergoing each procedure by number of cases of cystoid macular edema (CME).
 175 Total: The number of cases undergoing each procedure; OCT-evident CME: The number (and
 176 percentage) of cases with acute postoperative CME evident on ocular coherence tomography (OCT);
 177 CME Sympt: The number of cases who developed acute symptomatic postoperative CME; Late
 178 recurrence: The number of cases who developed acute postoperative CME (all of which were
 179 symptomatic); PPV ILM-peel (phakic): Eyes that underwent pars plana vitrectomy (PPV) and internal
 180 limiting membrane (ILM) peel; Combined (PE +PPV ILM-peel): Eyes that underwent simultaneous
 181 phacoemulsification (PE) with PPV and ILM-peel; Sequential 1 (PE 1st then PPV ILM-peel): Eyes that
 182 underwent PE and then subsequently underwent PPV and ILM-peel; Sequential 2 (PPV ILM-peel 1st
 183 then PE): Eyes that underwent PPV and ILM-peel and subsequently underwent PE. **P value. Result of**
 184 **ANOVA comparison between OCT-evident CME rates for, groups 2, 3 and 4 and group 1 (control). P**
 185 **< 0.05 was taken as statistically significant.**
 186

187 Figure 1.



Box-Whisker plot depicting LogMAR best-corrected visual acuity (BCVA) of all 4 groups preoperatively (preop VA) and 12 months (post-op) post-operatively. 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 5th and 95th percentiles.

Figure 2. Case study

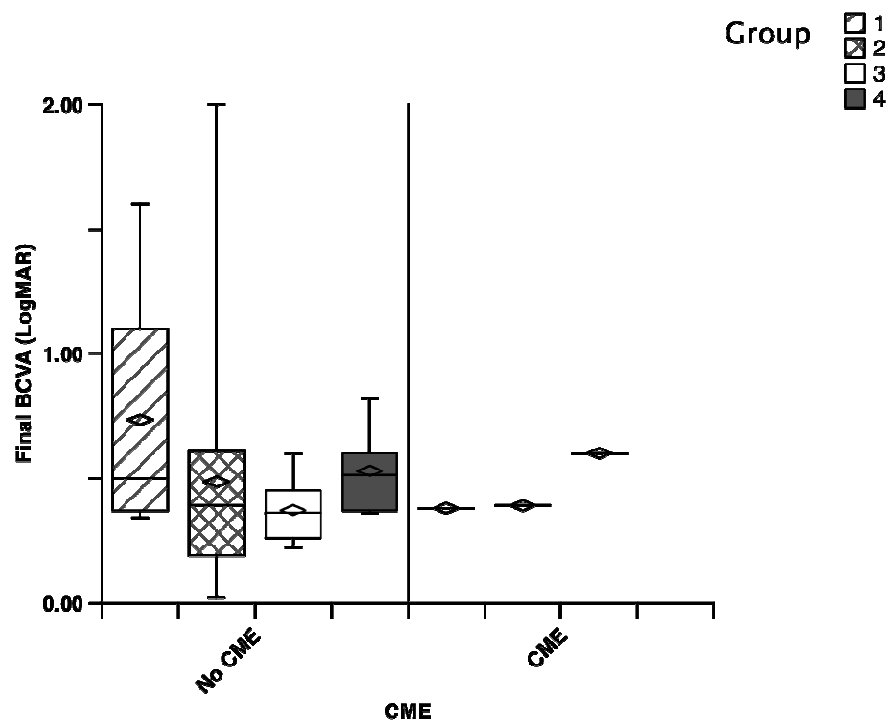


201

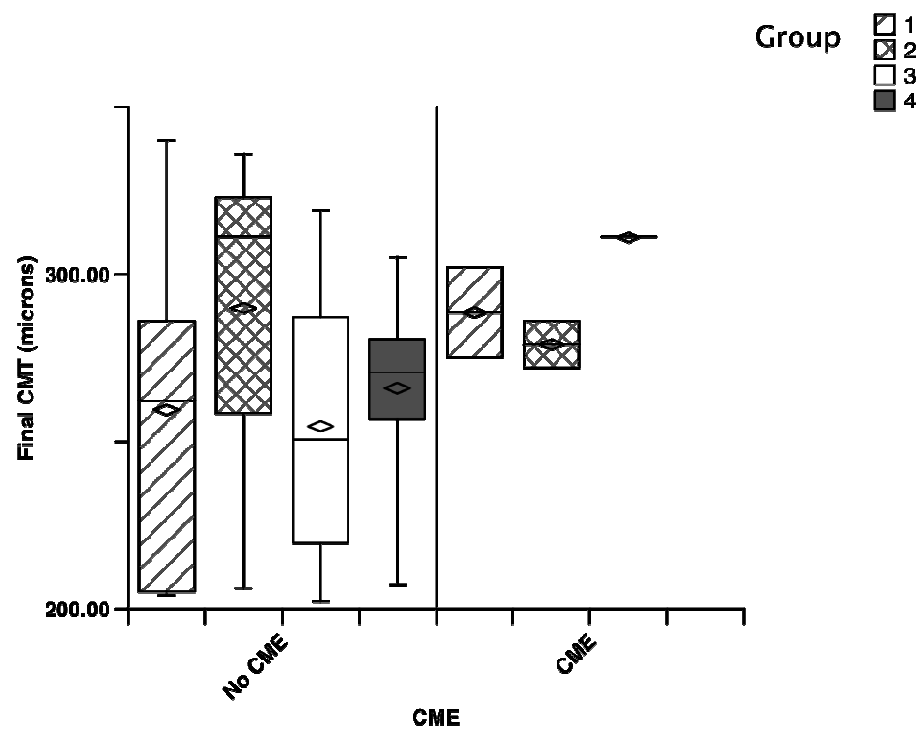
- 202 A. Optical coherence tomography (OCT) scan, left macula of a 61 year old female
 203 with reduced vision and metamorphopsia of 3 weeks duration, showing a grade 4
 204 full-thickness macular hole (FTMH). LogMAR best-corrected visual acuity (VA)
 205 of 0.48. This patient is from group 4.
 206 B. OCT scans of same eye 3 months post FTMH hole repair with pars plana
 207 vitrectomy and internal limiting membrane peel (PPV, ILM peel), showing a
 208 closed macular hole.
 209 C. OCT scan of same eye, 4 months post phacoemulsification (PE) demonstrating
 210 cystoid macular edema (CME).
 211 D. OCT scan of same eye 6 months post PE, after topical treatment with topical non-
 212 steroidal anti-inflammatories and topical steroids, showing resolution of CME.
 213

214 Figure 3.

215 A.



216 B.
217



218
219

Box-Whisker plot depicting A. final (12 month postoperative) LogMAR best-corrected visual acuity (BCVA) and B. final central macular thickness (CMT in μm) of 4 groups, based on development of post-operative CME. 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 5th and 95th percentiles.

References

1. Yonekawa Y, Kim IK (2012) Pseudophakic cystoid macular edema. *Current opinion in ophthalmology* 23 (1):26-32. doi:10.1097/ICU.0b013e32834cd5f8
2. Flach AJ (1998) The incidence, pathogenesis and treatment of cystoid macular edema following cataract surgery. *Transactions of the American Ophthalmological Society* 96:557-634
3. Cohen SM, Davis A, Cukrowski C (2006) Cystoid macular edema after pars plana vitrectomy for retained lens fragments. *Journal of cataract and refractive surgery* 32 (9):1521-1526. doi:10.1016/j.jcrs.2006.04.019
4. Schmier JK, Halpern MT, Covert DW, Matthews GP (2007) Evaluation of costs for cystoid macular edema among patients after cataract surgery. *Retina* 27 (5):621-628. doi:10.1097/01.iae.0000249577.92800.c0
5. Hayashi K, Igarashi C, Hirata A, Hayashi H (2009) Changes in diabetic macular oedema after phacoemulsification surgery. *Eye* 23 (2):389-396. doi:10.1038/sj.eye.6703022
6. Ram J, Gupta A, Kumar S, Kaushik S, Gupta N, Severia S (2010) Phacoemulsification with intraocular lens implantation in patients with uveitis. *Journal of cataract and refractive surgery* 36 (8):1283-1288. doi:10.1016/j.jcrs.2010.02.019
7. Henderson BA, Kim JY, Ament CS, Ferrufino-Ponce ZK, Grabowska A, Cremers SL (2007) Clinical pseudophakic cystoid macular edema. Risk factors for development and duration after treatment. *Journal of cataract and refractive surgery* 33 (9):1550-1558. doi:10.1016/j.jcrs.2007.05.013
8. de Nie KF, Crama N, Tilanus MA, Klevering BJ, Boon CJ (2013) Pars plana vitrectomy for disturbing primary vitreous floaters: clinical outcome and patient satisfaction. *Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie* 251 (5):1373-1382. doi:10.1007/s00417-012-2205-3
9. Mylonas G, Sacu S, Deak G, Dunavoelgyi R, Buehl W, Georgopoulos M, Schmidt-Erfurth U, Macula Study Group V (2013) Macular edema following cataract surgery in eyes with previous 23-gauge vitrectomy and peeling of the internal limiting membrane. *American journal of ophthalmology* 155 (2):253-259 e252. doi:10.1016/j.ajo.2012.07.013
10. Jalil A, Steeples L, Subramani S, Bindra MS, Dhawahir-Scala F, Patton N (2014) Microincision cataract surgery combined with vitrectomy: a case series. *Eye*. doi:10.1038/eye.2013.300

- 267 11. Li W, Sun G, Wu R, Wang X, Xu M, Sun C (2009) Longterm results after
268 phacovitrectomy and foldable intraocular lens implantation. *Acta ophthalmologica* 87
269 (8):896-900. doi:10.1111/j.1755-3768.2008.01383.x
- 270 12. Chan A, Duker JS, Ko TH, Fujimoto JG, Schuman JS (2006) Normal macular
271 thickness measurements in healthy eyes using Stratus optical coherence tomography.
272 *Archives of ophthalmology* 124 (2):193-198. doi:10.1001/archopht.124.2.193
- 273 13. Romano V, Angi M, Scotti F, del Grosso R, Romano D, Semeraro F, Vinciguerra
274 P, Costagliola C, Romano MR (2013) Inflammation and macular oedema after pars
275 plana vitrectomy. *Mediators of inflammation* 2013:971758. doi:10.1155/2013/971758
- 276 14. Kenawy N, Wong D, Stappler T, Romano MR, Das RA, Hebbar G, Prime W,
277 Heimann H, Gibran SK, Sheridan CM, Cheung YH, Hiscott PS (2010) Does the
278 presence of an epiretinal membrane alter the cleavage plane during internal limiting
279 membrane peeling? *Ophthalmology* 117 (2):320-323 e321.
280 doi:10.1016/j.ophtha.2009.07.024
- 281 15. Russo A, Costagliola C, Delcassi L, Parmeggiani F, Romano MR, Dell'Omo R,
282 Semeraro F (2013) Topical nonsteroidal anti-inflammatory drugs for macular edema.
283 *Mediators of inflammation* 2013:476525. doi:10.1155/2013/476525

284

285