**Title:**

*“Incidence of pseudophakic cystoid macular edema and OCT-detectable changes in central macular thickness* *in patients receiving prostaglandin analogues in the perioperative period: a prospective observational study”*

**Short running title*:***

*Incidence of pseudophakic cystoid macular edema in patients on prostaglandin analogues.*

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Presented at the ESCRS Barcelona, Spain. Meeting September 2015

**Financial disclosures:**

The authors have no financial disclosures to declare. No funding was obtained for this project.

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**Abstract:**

**Purpose:**

To define the incidence of cystoid macular edema (CME) and OCT-detectable subclinical changes in central macular thickness in patients using prostaglandin analogue (PGA) eyedrops after standard phacoemulsification surgery.

**Setting:**

An ophthalmic unit within a National Health Service (NHS) district general hospital in England.

**Design**:

Prospective observational study.

**Methods:**

Consecutive analysis of the incidence of postoperative CME after phacoemusification surgery by a single surgeon (E.S) was performed in eyes of patients using a PGA eyedrop. Presence of CME was determined clinically and using optical coherence tomography (OCT). All patients underwent uncomplicated cataract surgery. Exclusion criteria included eyes with preexisting pathology known to predispose to CME and eyes who had undergone previous ophthalmic surgery. A paired Wilcoxon signed ranks test was used to compare central retinal thickness measurements at baseline and three and six weeks postoperatively ascertaining statistical significance of any measured difference (P<0.05).

**Results:**

60 eyes of 48 patients were prospectively analyzed. Average patient age was 78.4 years. There were no cases of clinically significant CME. OCT-detectable subclinical CME was confirmed postoperatively in two eyes of two different patients (3.3% of operated eyes) 3 and 6 weeks postoperatively, respectively. Subclinical CME resolved in both cases within 8 weeks. In both cases, the difference in central retinal thickness at baseline and 6 weeks post-operatively was significant (*P<0.05*).

**Conclusion:**

The incidence of OCT-detectable subclinical CME following routine phacoemulsification surgery in patients using a PGA eyedrop throughout the perioperative period was 3.3%. There were no cases of clinical CME. These findings may help guide clinicians in their decision to continue or discontinue a PGA eyedrop in the perioperative period.

**Introduction:**

Cystoid macular edema (CME) is an important complication of modern cataract surgery and a primary cause of reduced vision post-operatively. Reported incidences vary widely, ranging from 0.1 to 2.35% (1-3). Peak incidence is around 4 to 6 weeks post-operatively (4).

CME is characterized by thickening of the central retina due to fluid accumulation in the outer plexiform layer and abnormal perifoveal retinal capillary permeability. Differing definitions of CME make it difficult to determine accurately its incidence (1, 5). CME is divided into clinical CME, associated with decreased visual acuity, and angiographic CME, referring to CME detected on fluorescein angiography or OCT without visual loss (1).

OCT provides a safe and non-invasive objective imaging modality for quantifying both clinical and subclinical CME (4, 6). An increase in macular thickness that is not clinically symptomatic or detectable by slit-lamp bio-microscopy has been noted using OCT following cataract surgery (7-9). Subclinical CME, characterized by perifoveal edema and cystic spaces on OCT without visual impairment has been described in several studies following uneventful phacoemulsification surgery (10, 11).

A number of ocular and systemic risk factors are known to contribute to the development of pseudophakic CME (5) and an increased risk has been reported in patients using a PGA eyedrop for glaucoma or ocular hypertension during the perioperative period. (6, 12-14), A large recent retrospective study was unable to associate a raised incidence of pseudophakic CME with PGA eyedrop usage (3). Some authors advocate discontinuing PGAs in the perioperative period, particularly in those patients deemed to be at higher risk of developing post-operative CME*,* including patients with pre-existing medical pathologies. These include previous retinal vein occlusion, uveitis, epiretinal membrane and/or diabetes (15).

To the best of our knowledge, there are no prospective studies evaluating the incidence of CME in patients undergoing phacoemulsification and IOL implantation whilst concurrently being treated with PGAs. Large variability in practice is observed in the UK with regards to PGA usage during the perioperative period. Ahad and Mckee’s questionnaire study on behalf of the Royal College of Ophthalmologists demonstrated that 60% of surgeons continue PGAs during the perioperative period (16).

Given the high volume of cataract surgery undertaken in the UK, the high prevalence of glaucoma and therefore the widespread use of PGAs amongst this patient demographic there is clearly a need to determine the safety profile of PGAs in the period following routine cataract surgery. We sought to objectively determine using clinical and OCT imaging modalities whether PGA use in the perioperative period was associated with an increased rate of post-operative clinical and subclinical CME development in a patient cohort using PGA eyedrops.

**Materials and Methods:**

Although no formal ethical review was required, approval for the study was granted by the local ethics committee review board. All patients provided written consent for cataract surgery in the format developed by the Royal College of Ophthalmologists and were provided with additional information about this study.

60 eyes of 48 patientsundergoing routine phacoemulsification surgery with posterior chamber IOL insertion and receiving a topical PGA were studied prospectivelybetween 1st of March 2010 and the 1st of January 2014. A single consultant surgeon (E.S) performed all cataract surgeries.

All study inclusion eyes were diagnosed with cataracts that still permitted a clear fundal view, and were using a topical PGA for control of intraocular pressure in the context of primary open angle glaucoma or ocular hypertension for at least one year prior to cataract surgery. All patients continued with the use of their PGA medication throughout the perioperative period. Patients deemed to be at higher risk of post operative CME were excluded (see table 1: inclusion/exclusion criteria).

Full ocular clinical examinations including BCVA using a standardized Snellen acuity chart, slit-lamp biomicroscopy, Goldmann applanation tonometry, and dilated posterior segment examination were performed at each visit. Central retinal thickness was recorded objectively to look for evidence of CME by Cirrus SD-OCT (Zeiss) scanning. Main outcome measures were presence of clinical CME or presence of subclinical CME.

SD- OCT examination was carried out by experienced technicians through a dilated pupil on the Zeiss Cirrus instrument. All OCTs were reviewed by the medical team to ensure scan quality.

The images obtained had a laminar structure with two bands of high intensity signal. The distance between the inner aspects of these bands was used as the measure of retinal thickness, in concordance with previous publications (17). Subclinical macular edema was defined as low-intensity cystic spaces within the laminar structure of the retina. This cystic change was not able to be seen with slit lamp biomicroscopic examination and not associated with reduced visual acuity. The acquired images were processed by the retinal map analysis of the OCT instrument (Zeiss Cirrus HD OCT Software). OCT imaging was undertaken pre-operatively on the day of surgery and repeated at 3 and 6 weeks post-operatively.

Preoperative and postoperative retinal thickness measurements measured by OCT in the study eyes were compared using a two tailed Wilcoxon signed rank (SPSS IBM Software Package). Pre operative retinal thickness was compared with postoperative thickness at 3 weeks and also separately with postoperative thickness at 6 weeks. P-values of less than 0.05 were considered statistically significant.

**Results:**

60 eyes of 48 patients were prospectively analyzed. Average patient age was 78.4 years with 65% of patients being female (n=39). Prostaglandin analogue usage of latanoprost was present in 42 eyes; Bimatoprost (Lumigan, Allergan) in 14 eyes; Bimatoprost/Timolol combination (Ganfort, Allergan) in 3 eyes; and Tafluprost (Saflutan, Santen) in 1 eye. Two eyes of two different patients (3.3%) were found to have subclinical CME with low intensity cystic spaces detected on OCT. No clinical CME was present, and slit-lamp biomicroscopy retinal examinations were normal. No reduction in visual acuity was seen.

OCT testing detected CME in the first case 3 weeks post operatively, and 6 weeks post-operatively in the second case. Both patients were using a branded version of latanoprost. Both patient’s OCT-detected CME resolved within 8 weeks using topical non-steroidal anti-inflammatory and topical steroid therapy (Bromfenac BD and prednisolone acetate ophthalmic suspension 1% two hourly during the day).

Mean preoperative central retinal thickness (CRT) was 254.6 µm (SD = 31.92 µm). Mean postoperative central retinal thickness was 267.7 µm at 3 weeks postoperatively (SD=30.85 µm). Mean central retinal thickness at 6 weeks postoperatively was 268.2 µm (SD=34.5 µm). Statistical significance was found between preoperative CRT and CRT at 6 weeks post operatively.

**Discussion**:

There is a lack of consensus with regards to PGA eyedrop use in patients undergoing cataract surgery (16) and it is not clear whether these drops are associated with an increased risk of CME. Previous authors have highlighted the lack of Oxford level 1 evidence on this subject (18). As cataract surgery is the most commonly performed elective surgical procedure in the UK (19) and PGA eyedrops are in widespread use, the risks associated with continuing PGAs post operatively needs to be accurately defined.

To our knowledge, this is the first prospective study investigating the incidence of CME following cataract surgery in patients using PGAs. Our study has provided incidence data for the rates of clinical and subclinical CME in a small cohort of patients using PGAs in the perioperative period. Although our sample size remains smaller than the aforementioned studies, our results suggests that PGAs can be used safely in the postoperative period without significantly altering the CME rate expected following routine phacoemulsification and IOL insertion.

Our findings concur with those of a large retrospective analysis of cataract surgical outcomes. In a subgroup analysis, Chu et found that PGAs did not increase risk of clinical CME. The incidence of CME in this study was 1.17% in patients without risk factors for CME (3). However, in this retrospective study, OCT or fluorescein angiographic imaging was only performed in symptomatic patients, in line with current UK clinical practice. The quoted incidence in this study therefore is likely to reflect the incidence of clinical CME with potential under-reporting of subclinical CME discussed by the authors (3), making direct comparison with our study difficult.

Ching et al described a cohort of 131 patients undergoing phacoemulsifiaction surgery with all patients having preoperative and postoperative OCT investigation. The CME rate was 3.05% (17), with all of these eyes exhibiting clinical CME. However that study included potential confounding factors, with 44 (33.6%) eyes with diabetes mellitus and 8 (6.11%) eyes that suffered posterior capsular breaks during surgery. We did not have any such cases. Conversely, the above study found retinal thickness to decrease post operatively.

Unlike previous studies, our study uses OCT to detect subclinical CME in patients using PGAs undergoing routine phacoemulsification and IOL insertion. The incidence of subclinical CME in this patient group had not been previously studied. A number of predisposing risk factors for CME development are well known. With the use of our exclusion criteria, our patient cohort has allowed us to more accurately establish the role PGAs may play in post-operative CME. The aim was to eliminate as many confounding factors as possible, including ensuring standard operating procedures, the same operating surgeon and identical surgical equipment.

A weakness of our study is that no control group is available. Although this would aid comparison within our own study, the authors feel that the incidence of OCT proven CME has been investigated by others (17). A larger sample size may more accurately define the incidence of CME. Central corneal thickness (CCT) was not measured in study participants. It has been postulated that increased CCT may limit the amount of PGA penetration into the anterior chamber (20).

The results from our small patient cohort however provide the highest level of evidence available to date on this topic. Further multicentre, case-controlled studies are required to further establish the role of PGAs in CME development in the perioperative period, and aid development of a working guideline for cataract surgeons. The results of such a study would aid decision making in a large number of patients undergoing cataract surgery.

**What was known?:**

* The incidence of CME following cataract surgery is highly variable, with a published incidence of between 0.1% and 2.35 %. Peri-operative usage of a PGA eyedrop has been reported to contribute to development of postoperative CME.
* A recent large retrospective study did not show increased risk of CME with PGA use at time of cataract surgery (3).
* Prospective studies ascertaining whether usage of PGAs increases the risk of post-operative CME are limited.
* There is currently no agreed consensus on the use of PGAs in the perioperative period.

**What this paper adds?:**

* Incidence of OCT-detectable subclinical pseudophakic CME in patient eyes treated with a PGA in the peri-operative period is 3.3% in our cohort.
* This prospective study may help surgeons decide whether to continue or discontinue a PGA eyedrop in the peri-operative period.

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