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New observation of microcystic macular edema as a mild form of cystoid macular lesions after standard phacoemulsification

Prevalence and risk factors

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Abstract

We present the new observations of postoperative microcystic macular edema (MME) as a mild form of cystoid macular lesions (CMLs) after standard phacoemulsification.

To report the incidence, risk factors, and pathophysiology of MME compared to conventional concept of pseudophakic cystoid macular edema (CME), we retrospectively reviewed patients' records. Pseudophakic CMLs were defined as any cystic fluid collections that were newly formed after cataract surgery, confirmed by preoperative and postoperative optical coherence tomography (OCT) examinations. CMLs were classified into 2 groups, which are CME and MME, according to the change the central retinal thickness. The dataset consisted of 316 patients (mean age, 67.52 ± 12.95 years; range, 42–87 years). Topical nonsteroidal anti-inflammatory drug (NSAID) were administered in 197 eyes during the perioperative period; 147 eyes were not treated. CMLs were present in 22 out of 344 (6.39%) eyes. Six of 344 eyes (1.74%) had CME and 16 of 344 eyes (4.65%) had MME. The incidence of MME significantly decreased in the group of patients treated with topical NSAIDs ($P = .039$), while the incidence of CME was not different in both groups ($P = .408$). All of the patients with MME were experienced improvement with only topical NSAIDs. However, 67% (4/6) of patients with CME did not improve with topical NSAIDs alone and needed additional treatments. Pseudophakic MMEs were more likely to have a history of diabetic retinopathy, epiretinal membrane, and eyes were not treated with topical NSAID.

This study showed a wide clinical spectrum of CMLs. MME has not been included in the conventional definition of pseudophakic CME. Topical NSAIDs could decrease the CML incidence. People with risk factors for CML should use topical NSAIDs and undergo regular follow-up OCT examinations.

Abbreviations: BCVA = best corrected visual acuity, CME = cystic macular edema, CML = cystoid macular lesion, CST = central subfield thickness, INL = inner nuclear layer, IOP = intraocular pressure, MME = microcystic macular edema, NSAID = nonsteroidal anti-inflammatory drug, OCT = optical coherence tomography.

Keywords: nonsteroidal anti-inflammatory drug, phacoemulsification, pseudophakic cystoid macular edema

1. Introduction

Cataract surgery is one of the most commonly performed surgical procedures in developed countries. The surgical methods have improved over the years, thereby decreasing the incidence of complications and increasing patients' expectations of successful surgical outcomes. Postoperative cystoid macular edema (CME) is the most common cause of less-than-expected postoperative visual outcomes after cataract surgery.[1,2] Incidence rates of CME vary substantially throughout the literature, depending on which definition is used.[3] Clinically significant CME has a reported incidence of 1% to 2.35% after cataract surgery.[4,5] The presence of CME can be determined in 3 ways: angiographic examination, clinical examination, and optical coherence tomography (OCT). OCT is a diagnostic tool that allows objective quantification of the spectrum of CME by directly measuring changes in the volume of the retina.[6–9] The incidence of CME measured by OCT is as high as 41%.[10] OCT is the most sensitive way to detect CME, followed by angiography, and then clinical examination, which is the least sensitive. Antcliff et al[7] compared OCT with fundus fluorescein angiography for detecting CME and found that the sensitivity was 96% and the specificity was 100% for OCT. Therefore, fluorescein angiography has been replaced by OCT as the major test to diagnose and monitor CME. CME after cataract surgery is characterized by hyperpermeability of the macular capillaries resulting in excessive fluid in the retina and polycystic expansion of the extracellular spaces.[11,12] Recently, many authors have reported microcystic edema (MME) in the central macula of multiple sclerosis (MS) and optic neuropathy of various etiologies predominantly involving the inner nuclear layer (INL).[13–16] Isolated INL cystoid changes in the absence of outer

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plexiform morphology have been reported in a subset of these processes.[17–19] Burggraaff et al[20] reported the clinical spectrum of MME and indicated that postoperative MME was the second most common cause of MME. However, until now, there have been no reports regarding the incidence of postoperative MME. We suspected that MME-like cystic lesions might occur as a mild form of conventional postoperative CME involving microcystic lesions and INL without retinal thickening. In this study, we reviewed the records of patients who underwent uneventful cataract surgery and analyzed the incidence and risk factors of cystic macular lesions (CMLs), which included conventional CME lesions and MME-like microcystic lesions on their postoperative OCT images.

2. Methods

This retrospective chart review involved consecutive patients who had phacoemulsification and were treated postoperatively at the Kyungpook National University Hospital, Daegu, Korea, from October 2013 to June 2015. The study was approved by the Institutional Review Board and was conducted in compliance with all patient privacy regulations. All patients received moxifloxacin 4 times per day for 2 weeks and prednisolone 1% drops (started on day 0) 6 times per day for 3 days and 4 times per day for 2 weeks. One hundred ninety-seven eyes of 189 patients were treated with topical bromfenac sodium hydrate (Bronuck; Taejoon Pharm. Ltd.) twice per day starting 1 day before surgery and continued for 2 weeks after surgery. Data collection included sex, age, and preexisting ocular and systemic diseases. Patients were excluded if they had complicated cataract surgery (e.g., significant corneal edema, posterior capsule rupture, vitreous loss, dropped nuclear material, retained cortical material, or an intraocular lens [IOL] not placed in the capsular bag).

All phacoemulsification surgeries were performed by the same physician (K.H.K.) using the Infiniti phaco machine (Alcon Labaratories, Inc.). Ocular examinations (best corrected visual acuity [BCVA], intraoperative pressure [IOP], anterior segment, and retinal examination), including OCT measurements, were performed and recorded preoperatively and 4 weeks and 12 weeks postoperatively. All OCT imaging was performed using spectral-domain optical coherence tomography (SD-OCT; Spectralis; Heidelberg Engineering, Heidelberg, Germany and Spectral OCT/SLO; OTI Ophthalmic Technologies Inc, Miami, FL). The best-quality macular cube images of all scans performed during each visit were chosen and tabulated. Any areas of interest were imaged using the detailed program of the OCT device. All patients underwent imaging at baseline and the 4-week and 12-week follow-up examinations. Specifically, central subfield thickness (CST; mm) measurements were collected from each patient for statistical analysis.

2.1. Definition of pseudophakic cystic macular lesions

We defined pseudophakic CMLs as any cystic fluid collections that were newly formed after cataract surgery. Lesions were confirmed with OCT. CMLs were classified into 2 groups: CME and MME. CME was defined as multiple cyst-like (cystoid) hyporeflective areas of fluid in the macula with increased macular thickness, whereas MME was defined as cystic lacunar areas of hyporeflectivity with clear boundaries in the INL without any change in the macular thickness (Fig. 1).

The difference in the incidence of CMLs between two groups was analyzed using Fisher exact test and χ^2 test. The independent *t*-test was used for comparisons between the 2 groups for variables with ordered-response categories (central subfield thickness, visual acuity). We evaluated the relationship of topical NSAIDs with the risk of pseudophakic MMEs using conditional logistic regression analysis to estimate the adjusted odds ratio (OR) and 95% confidence interval (CI). Variables examined as potential confounding factors included patient age, epiretinal membranes, glaucoma, uveitis, diabetic retinopathy, and vascular occlusion. $P < .05$ was considered significant.

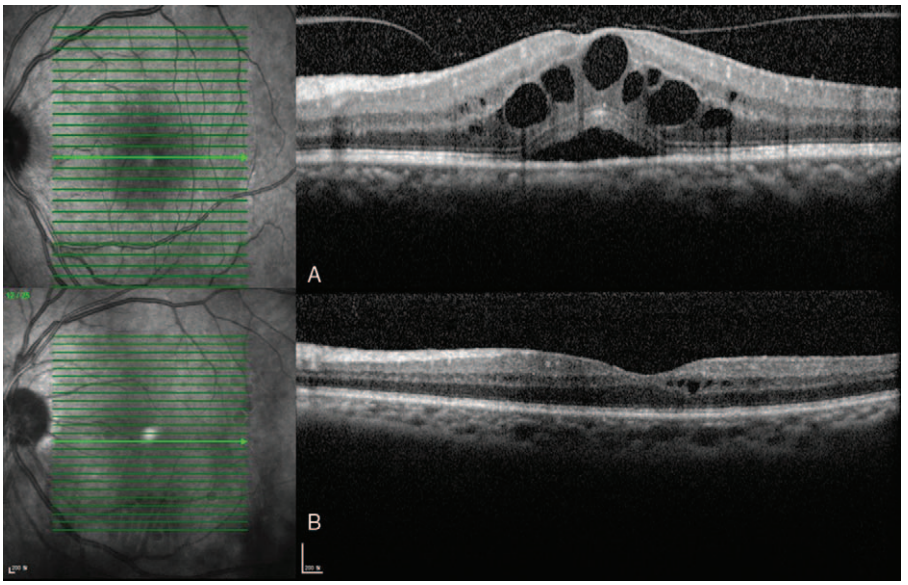

Figure 1. Cystic macular lesions were classified into 2 groups. A, Cystoid macular edema (CME) includes multiple cyst-like (cystoid) areas of fluid appearing in the macula and causing retinal swelling or edema. B, Microcystic macular edema (MME) is defined as cystic lacunar areas of hyporeflectivity with clear boundaries in the inner nuclear layer (INL) without changing the macular thickness.

Table 1

Patient demographics and clinical characteristics.

	Total eyes (n = 344)	Patients treated with topical NSAIDs (n = 197)	Patients not treated with topical NSAIDs (n = 147)	P
Age (ys) (Mean ± SD)	67.47 ± 13.28	67.99 ± 11.80	66.70 ± 14.91	.37
Sex, n (%)				
Male	172 (50%)	105 (53.3%)	67 (45.6%)	.16
Female	172 (50%)	92 (46.7%)	76 (51.7%)	
Comorbidity, n (%)				
DM	72 (20.9%)	42 (21.3%)	30 (20.4%)	1.00
Hypertension	136 (39.5%)	73 (37%)	63 (42.8%)	.38
Glaucoma	28 (8.1%)	13 (6.6%)	15 (10.2%)	.32
Uveitis	10 (2.9%)	3 (1.5%)	7 (4.7%)	.11
RVO	13 (3.8%)	5 (2.5%)	8 (5.4%)	.25
ERM	21 (6.1%)	10 (5.1%)	11 (7.5%)	.50

DM = diabetes mellitus, ERM = epiretinal membrane, RVO = retinal vacular occlusion.

3. Results

Reviews of 344 eyes of 316 patients were performed, including 197 eyes treated with topical NSAIDs; 147 eyes were not treated with topical NSAIDs. All patients had at least 3 months of follow-up. The ages of the patients ranged from 42 to 87 years (mean, 67.2 ± 14.2 years). Baseline characteristics of patients who underwent uncomplicated standard phacoemulsification are presented in Table 1.

3.1. Incidence of CMLs

Among the 344 eyes with uncomplicated standard phacoemulsification, we ascertained 22 CML cases (6.39%). Six of 344 eyes (1.74%) had CME and 16 of 344 eyes (4.65%) had MME. The incidence of CME after cataract surgery was 2.72% (4 eyes) for patients not treated with topical NSAIDs and 1.01% (2 eyes) for those using topical NSAIDs ($P = .408$, Fisher exact test). Eleven eyes (7.48%) had MME in the group of patients not treated with topical NSAIDs; 5 eyes (2.53%) had MME in the group of patients treated with topical NSAIDs ($P = .039$). The incidence of CMLs was significantly lower for topical NSAID-treated patients. (10.2% vs 3.55%; $P = .015$) (Table 2).

3.2. Alteration of CST

The CST (μm) ± SD values among the 22 CML cases confirmed with OCT were 271 ± 16, 306 ± 34, 293 ± 48 before surgery and at 4 weeks and 12 weeks after surgery, respectively. Six cases of CME had OCT CST (μm) ± SD values of 273 ± 32, 380 ± 24, and 313 ± 32, whereas 16 cases of MME had OCT CST values of 271 ± 19, 279 ± 25, and 286 ± 27 before surgery and 4 weeks and 12 weeks after surgery, respectively. Postoperative CST values of topical NSAID-treated patients were significantly lower than those of untreated patients at 4 weeks ($P = .002$) and 12 weeks ($P = .020$) (Table 3).

3.3. Alteration of visual acuity

For the 22 CML cases, BCVA (logMAR) ± SD values before surgery and 4 and 12 weeks after surgery were 0.62 ± 0.12, 0.28

Table 2

Incidence of CME and MME.

	Total eyes (n = 344)	Patients treated with topical NSAIDs (n = 197)	Patients not treated with topical NSAIDs (n = 147)	P
CME	6 (1.74%)	2 (1.01%)	4 (2.72%)	.408[a]
MME	16 (4.65%)	5 (2.53%)	11 (7.48%)	.039[b]
Total (CMLs)	22 (6.39%)	7 (3.55%)	15 (10.2%)	.015[b]

CME = cystoid macular edema, CMLs = cystoid macular lesions, MME = microcystic macular edema.
[a] Fisher exact test.
[b] Chi-square test.

Table 3

Change in central subfield thickness after cataract surgery.

	Total eyes (mean (μm) ± SD)	Patients treated with topical NSAIDs (mean (μm) ± SD)	Patients not treated with topical NSAIDs (mean (μm) ± SD)	P
Preoperative CST	268 ± 34	267 ± 33	270 ± 35	.418[a]
Postoperative CST				
4 weeks	280 ± 44	272 ± 41	287 ± 47	.002[a]
12 weeks	283 ± 46	276 ± 32	289 ± 58	.020[a]

CST = central subfield thickness.
[a] Independent *t*-test.

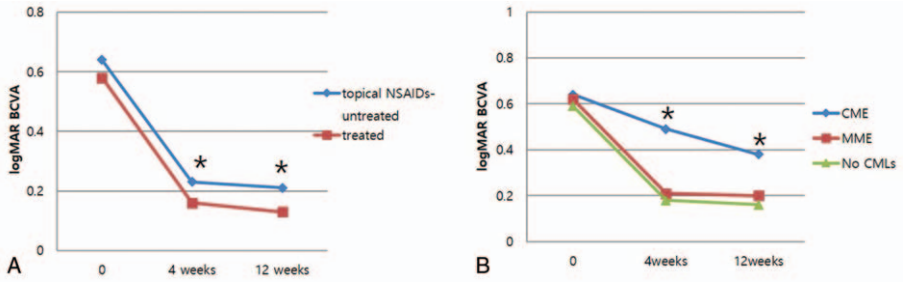

Figure 2. A, Alteration of logMAR best corrected visual acuity (BCVA) after phacoemulsification for the 2 groups. B, Alteration of logMAR BCVA after phacoemulsification for cystic macular edema (CME) and microcystic macular edema (MME) cases. The asterisk (*) indicates a statistically significant difference between the groups of eyes at each time point ($P < .05$).

± 0.37, and 0.24 ± 0.26, respectively. Among the CMLs, 6 CME cases had BCVA (logMAR) $\pm$ SD values of 0.64 ± 0.26, 0.49 ± 0.19, and 0.38 ± 0.32, respectively, and 16 MME cases had BCVA (logMAR) $\pm$ SD values of 0.62 ± 0.27, 0.21 ± 0.34, 0.20 ± 0.16 before surgery and 4 weeks and 12 weeks after surgery, respectively. Eyes that developed CME had significantly worse BCVA than eyes that developed MME at 4 weeks ($P < .001$) and 12 weeks ($P < .001$). Postoperative BCVA of topical NSAID-treated patients was significantly better than that of untreated patients at 4 weeks ($P = .003$) and 12 weeks ($P = .002$) (Fig. 2).

3.4. Risk factors of MMEs

During univariate analysis, those with pseudophakic MMEs were more likely to have a history of diabetic retinopathy, epiretinal membrane, and eyes were not treated with topical NSAID. After adjusting for patient demographics and systemic and ocular comorbidity, the OR for the association of MMEs with no prophylactic treatment of topical NSAID was 4.02 (95% CI, 1.17–13.85). History of diabetic retinopathy (OR, 8.34; 95% CI, 2.58–26.97), epiretinal membrane (OR, 14.94; 95% CI, 3.63–61.56) were associated with the risk of pseudophakic MMEs.

3.5. Treatment of CMLs

Topical NSAIDs were found to be effective for the treatment of MME. All (16/16) of the patients with MME experienced improvement with only topical NSAIDs after cataract surgery. For patients with CME, 67% (4/6) of patients did not improve with topical NSAIDs alone and needed additional treatments. Four eyes with refractory CME treated with topical NSAIDs required at least 1 intravitreal injection of triamcinolone or bevacizumab. At 12 weeks, 3 eyes (75%) showed improvements in BCVA from 0.49 to 0.38, and OCT data demonstrated a significant reduction in CST from 380 μm to 313 μm.

4. Discussion

Pseudophakic CME results from inflammation and subsequent breakdown of the blood–aqueous barrier after cataract surgery. Diagnostic criteria for pseudophakic CME have not been defined in relation to long-term visual outcomes, and definitions vary substantially in the literature. Conventionally, pseudophakic CME is classified as angiographic (seen on fluorescein angiography) or clinical (associated with decreased visual acuity) and acute (within 6 months) or chronic (more than 6 months).[21] However, OCT definitions for CME have been recently added and the incidence of pseudophakic CME varies between 0.2% and 20%[3] depending on the definition used for diagnosis, which include clinical, angiographic, and OCT. In our large, retrospective, single-center study, we defined the CMLs using OCT definition, the prevalence of CME was 1.75% (n = 6), which is similar to that of previous studies, but the incidence of whole CMLs was slightly greater than that of previous studies.[22,23]

Microcystic changes were most frequently observed with age-related macular degeneration, after vitrectomy, after cataract surgery, and in epiretinal membranes.[20] We reviewed the incidence of pseudophakic MME by defining it as CMLs without a change in retinal thickness, which were not included in the definition of conventional pseudophakic CME.[4]

Topical NSAIDs act on the inflammatory cascade, which is presumed to cause postoperative macular edema. Our study showed that the incidence rates of MME were lower for patients treated with topical NSAIDs. Additionally, all patients with MME recovered completely with topical NSAIDs, and these results suggest that MME is caused by an intraocular inflammatory reaction.

Risk factors predisposing to the development of pseudophakic CME have been extensively studied. Diabetes, hypertension, epiretinal membrane, uveitis, glaucoma, and vascular occlusion can be related to the incidence of pseudophakic CME.[24–26] Our data showed risk factors for CME and MME that are similar to those previously reported.

Although the clinical courses would be different between CME and MME, the incidence, risk factors, and prophylactic response to topical NSAIDs by MME were very similar to those of CME. This suggests that MME is not a new postoperative complication, but rather a mild form of CME. CMLs have a clinical spectrum of increased retinal vascular permeability by inflammatory reactions triggered by cataract surgery. CME involves a severe form of CML, whereas MME involves a mild form.

This study has some limitations. First, this study was conducted retrospectively. Follow-up examinations and schedule were not fully standardized. It could affect the incidence of CMLs. Prospective designed follow-up studies with more patients are needed. Second, this study failed to obtain a histological sample and could not accurately infer the pathophysiological process of MME. Despite these limitations, we believe this is the first study to define the concept of pseudophakic MME and to review the incidence of pseudophakic MME after cataract surgery. Our study showed that OCT allows cross-sectional observation of MME, which is difficult to diagnose by slit-lamp examination or fluorescein angiography. We think that sensitivity and detection rates of postoperative CMLs will increase with OCT.

In summary, this retrospective study defined the concept of MME and reviewed the incidence for 12 weeks after phacoemulsification. These findings will allow clinicians to counsel patients more accurately regarding the risks and results of pseudophakic CMLs when undergoing cataract surgery and to recommend periodic OCT examinations because MME was not identified by clinical examination or fluorescein angiography. These study results will be valuable for assigning the resources needed for better management of pseudophakic CMLs, particularly as topical NSAIDs are used in routine clinical practice.[27–29].

Author contributions

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Writing – original draft: Dong Hee Yoon, Hong Kyun Kim.
Writing – review & editing: Dong Jin Kang, Myung Jun Kim, Hong Kyun Kim.
Investigation: Myung Jun Kim, Hong Kyun Kim.
Visualization: Myung Jun Kim.
Conceptualization: Hong Kyun Kim.
Funding acquisition: Hong Kyun Kim.
Resources: Hong Kyun Kim.
Supervision: Hong Kyun Kim.

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