Abstract: Pseudophakic cystoid macular edema (PCME) is the most common complication of cataract surgery and is one of the possible causes of low visual acuity after cataract surgery. Various factors are implicated in its development but the core mechanism is likely surgically induced anterior segment inflammation that results in the release of endogenous inflammatory mediators. Anti-inflammatory medicines, including steroid and nonsteroid anti-inflammatory drugs, are postulated as having a role in both the prophylaxis and treatment of PCME. This article presents an updated review on the pathogenesis, risk factors, prophylaxis and treatment in PCME that reflect current research and practice.

Key words: cataract; cyclooxygenase inhibitors; macular edema; prostaglandins

Sažetak: Cistoidni makularni edem komplikacija je nakon operacije katarakte i najčešći je uzrok loše vidne oštrine nakon operacije katarakte. Različiti su patofiziološki mehanizmi nastanka makularnog edema, ali najčešće se dovodi u vezu s postoperativnom upalom pri kojoj se oslobađaju medijatori upale i dovode do nakupljanja tekućine u području makule. Protuupalni lijekovi, uključujući steroide i nesteroidne antireumatike, imaju veliku ulogu u profilaksiji i terapiji cistoidnog makularnog edema. U ovom preglednom članku prikazani su najnoviji stavovi o patogenetskom mehanizmu nastanka edema, rizičnim faktorima, profilaksiji i terapiji, proizšli iz istraživanja i kliničke prakse.

Ključne riječi: inhibitori ciklooksigenaze; katarakta; makularni edem; prostaglandini

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Cystoid macular edema (CME) is a painless condition in which swelling or thickening occurs of the central retina and is usually associated with blurred or distorted central vision. Less common symptoms include metamorphopsia, micropsia, scotomata, and photophobia. The pseudophakic cystoid macular edema (PCME), also known as Irvine Gass syndrome, was first reported by A. Ray Irvine Jr. in 1953 and later elucidated with fluorescein angiography by J. Donald M. Gass in 1969 and is one of the possible causes for low visual acuity after cataract surgery. Despite advances in cataract surgery, such as microincision and new phacoemulsification techniques, CME may occur even in uncomplicated surgeries. American studies show that angiographic edema may occur in 60% of intracapsular surgeries, varying between 15-30% in extracapsular surgeries, and 4-11% in phacoemulsification. Clinical CME, on the other hand, occurs in only 0.1 to 2.35% of patients. Pseudophakic cystoid macular edema is the most common complication of cataract surgery. The detection of CME can be either through clinical examination, angiographic examination or optical coherence tomography examination. Increased patient expectations and increased quality of vision issues have dictated that measures we used in the past were really inadequate to describe the visual loss associated with CME. Of the three techniques, optical coherence tomography (OCT) has the highest sensitivity, followed by angiography and then clinical examination. Therefore, the incidence of PCME varies depending on which technique is employed. In the past, the incidence of clinical macular edema was 1 percent to 2 percent. The detection of CME with sensitive instruments does not always correlate to visual acuity The incidence of PCME with reduced vision measured by OCT is up to 14 percent. The incidence of CME measured by OCT and fluorescein angiogram after uneventful cataract surgery is up to 41 percent and 30 percent. Because of the heterogeneity of definitions and diagnostic criteria, its incidence has been reported to be between 1% and 30%, with, however, an incidence of 1%–2% of clinically significant PCME in patients with no risk factors. Although in most cases, PCME is a self-limiting disorder; in rare cases, it can lead to long-term visual deterioration that is difficult to treat. Thus, it is important to discuss recent studies on PCME prevention and treatment measures, as well as the recommendations of major ophthalmic societies.

Various factors have been implicated in pseudophakic cystoid macular edema (PCME) development but the core mechanism is surgically induced anterior segment inflammation that results in the release of endogenous inflammatory mediators.

**PATHOGENESIS FOR CME**

Although PCME was described many years ago, its pathophysiology remains uncertain and a multitude of mechanisms have been suggested. The pathogenesis of PCME appears multifactorial based on experimental studies and clinical observations. Various factors have been implicated in its development such as inflammation, vascular instability, vitreomacular traction, ocular hypotonia and light toxicity. The core mechanism is likely surgically induced anterior segment inflammation that results in the release of endogenous inflammatory mediators. Prostaglandins, cytokines and other vasopermeability factors disrupt the perifoveal retinal capillaries, resulting in fluid accumulation. Inflammation due to surgical manipulation seems to be the main cause. Surgically induced trauma to the iris, ciliary body and lens epithelium disrupts the blood-aqueous barrier resulting in release of prostaglandins, vascular endothelial growth factor, insulin-like growth factor-1 and other inflammatory mediators. Inflammatory mediators increase vascular permeability and transudates accumulate in the external plexiform layer and inner nuclear layer, forming cysts. It is postulated that surgical manipulation within the anterior chamber may lead to the release of arachidonic acid from uveal tissue, with the production of either leukotrienes via the lipoxygenase pathway or prostaglandins (PGs) via the cyclooxygenase (COX) pathway. It is not clear why the fluid leaking from the perifoveal capillaries accumulates within the macula,
despite the massive production and distribution of inflammatory cytokines throughout the retina. The reduced fluid reabsorption within the macula may be explained, at least in part, by the absence of blood vessels within the avascular zone combined with the high metabolic activity of the fovea. This observation implies that the degree of inflammation determines the severity of PCME, which can range from very mild to clinically significant forms.

### RISK FACTORS FOR CME

Many local, systemic, and surgery-related conditions increase the risk of PCME. The duration, severity, type of diabetes, hardness of the lens, and glycated hemoglobin-HbA_{1c} were risks for PCME in diabetic patients after cataract surgery. A 40% or more increase in foveal thickness and 20% or more decrease in macular sensitivity offer an objective and reliable diagnostic standard to report PCME in diabetics.

In a study by Perente et al, the central macular thickness (CMT) measured by using OCT increased significantly between 1 and 6 months postoperatively. In the study conducted by Von Jagow et al., a moderate increase in macular thickness between the first and sixth week after surgery was observed, but there was no significant correlation between CMT and the best-corrected visual acuity (BCVA). Sahin et al reported that a moderate CME increase in the first 3 postoperative months did not cause vision impairment in patients without PCME and that macular thickness gradually decreased to baseline values by the end of the 3-month period. Akcay et al observed higher macular thickness in patients after complicated cataract surgery than in those whose procedure had been uneventful. CME incidence increases when surgical complications, such as the posterior capsular rupture, vitreous loss, incarcerated vitreous in the incision, cortical remnants in the vitreous, trauma to the iris, intraocular lens dislocation, iris fixation or anterior layer intraocular lens and premature posterior capsulotomy, occur. Pre-existing retinal diseases such as retinal vein occlusion and vitreoretinal interface changes, such as the epiretinal membrane, pose a bigger risk of CME. Special attention must be paid to diabetic patients. In these cases, it is extremely difficult to differentiate between CME and diabetic macular edema since diabetic macular edema patients tend to have worse vision after cataract surgery. Patients with prior treated macular edema, regardless of treatment choice, and patients with non-central-involved macular edema are at greater risk of worsening conditions although there is controversy regarding the risk of diabetic retinopathy progression. For practical purposes, patients suffering from central-involved or non-central-involved macular edema, history of previously treated macular edema and severe retinopathy should be properly treated before surgery. Patients with uveitis are also more likely to develop CME compared to normal patients. Strict control of the inflammation before surgery and great attention after surgery is advisable. In glaucoma patients, the use of prostaglandin drops is linked to a higher incidence of CME.

### DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS FOR CME

Modern cataract surgery is an efficient procedure and is generally associated with good visual results. Reduced visual acuity following cataract surgery is the most common clinical finding in PCME. Clinical CME appears on average from 4 to 6 weeks after surgery. Patients may complain of metamorphopsia, central scotoma and reduced contrast sensitivity. Refraction may show a hyperopic shift. Clinical examination shows loss of the foveal depression and retinal thickening. Intraretinal parafoveal cysts may be observed. Fluorescein angiography can help by showing perifoveal capillary leakage at the early stages, as well as telangiectasias and capillary dilation. Optic nerve impregnation is frequent and extremely important in the differential diagnosis of other causes of CME. Optical coherence tomography use has been widespread and its sensitivity works well in detecting macular edema. This test can show hyporeflexia lesions compatible with intraretinal fluid, loss of foveal depression and retinal thickening. OCT is also used to show other changes in the vitreoretinal interface, such as epiretinal membranes and lamellar holes, which may influ-
ence the prognosis\textsuperscript{24,25}. It is important to differentiate PCME from a possible subretinal neovascular secondary to macular degeneration related to age.

**PROPHYLAXIS FOR CME**

Prevention of PCME includes the least invasive surgery possible with no complications, short surgery time, and in some cases, the use of anti-inflammatory pharmacological agents. With the advancement of surgical technique and the improvement of surgical outcome, one of the main concerns for surgeons is to avoid or treat CME in pseudophakic patients\textsuperscript{5}. Atraumatic surgery itself may be considered a prophylactic measure for edema\textsuperscript{26}. Currently no standardized protocol exists for the prophylaxis and management of PCME because of a lack of prospective randomized clinical trials. Therapeutic interventions are based on the proposed pathogenesis of edema, mainly inflammation and vitreous traction. In an attempt to reduce the risk of postoperative CME, all pre-existing ocular conditions should be controlled prior to cataract surgery. Eyes with diabetic retinopathy should have appropriate evaluation and management. Uveitic eyes should have adequate inflammation control for at least three months prior to proceeding with cataract surgery.

**TREATMENT FOR CME**

The aim of treatment is to contain the inflammatory cascade which leads to blood-retinal barrier, resulting in intraretinal fluid accumulation. Treatment should begin by removing post-surgical factors predisposing to CME. Most cases are spontaneously solved, even without treatment. However, it is not possible to predict which cases will become chronic and should be treated as acute (up to 4 months after onset) and which could go untreated. It is difficult to establish an evidence-based conduct for prophylaxis and therapy of PCME. **Topical non-steroidal anti-inflammatory drugs (NSAIDs)** are frequently used in the prophylaxis and treatment of PCME. Currently NSAIDs are approved by the Food and Drug Administration for postoperative inflammation only. NSAIDs are potent inhibitors of prostaglandins, a vital mediator in CME development. In addition to NSAIDs, **topical corticosteroids** are commonly used in prophylaxis and treatment. Studies reporting the efficacy of corticosteroids in PCME are often confounded by concomitant topical NSAID administration. It does appear that combination therapy with topical NSAID and corticosteroid may be superior to either individual therapy. Corticosteroids and topical NSAIDs, either as monotherapy or combined therapy, are a commonly used first-line treatment approach\textsuperscript{27}. When this approach is ineffective, intravitreal application of corticosteroids and anti-vascular endothelial growth factor (VEGF) agents may be an option. **Vascular endothelial growth factor** causes breakdown of the blood-retinal barrier and increased vascular permeability, contributing to the development of macular edema. Anti-VEGF with intravitreal bevacizumab has been shown effective in refractory PCME. Almeida et al in a prospective, placebo-controlled, parallel-assignment, double-masked, randomized clinical trial compared the effect of topical nepafenac 0.1%, ketorolac 0.5%, and placebo on PCME in patients after modern-day phacoemulsification surgery with posterior chamber intraocular lens implantation\textsuperscript{8}. The patients used one of the aforementioned substances four times daily for 4 weeks, starting 1 day before the planned surgery. In addition, all patients were administered prednisolone acetate 1.0% eyedrops four times daily over the first week postoperatively. The dose was then tapered by one drop every week. The OCT performed at baseline and at 4 weeks postoperatively did not show a significant retinal thickening in subjects treated with NSAIDs. While a mild CME increase in placebo eyes was noted, at 4 weeks there was no significant difference in the ultimate visual acuity between the groups. The study concluded that in low-risk patients, the use of topical nepafenac or ketorolac does not seem to offer benefit over placebo in preventing OCT changes indica-
tive of macular edema after surgery. Other authors found no significant differences between diclofenac 0.1% and ketorolac 0.45% groups in macular thickness 1 month after uneventful surgery. However, at the second postoperative month, the ketorolac group had significantly lower central subfield thickness than the diclofenac group. Wang et al compared the efficacy of bromfenac 0.1% administered twice daily for 4 weeks, bromfenac 0.1% administered twice daily for 8 weeks, fluorometholone 0.1% administered three times daily for 4 weeks, and dexamethasone 0.1% administered three times daily for 4 weeks. All patients also received 15 mg of prednisone in one daily dose for 7 days postoperatively. No topical anti-inflammatory drugs were used preoperatively. At 2 months, the mean OCT-based retinal thickness was significantly lower in both bromfenac groups. However, there were no significant differences in visual acuity between the groups. Wittppen et al in a randomized and masked comparison, reported a low incidence of OCT-confirmed PCME in low-risk patients treated with prednisolone acetate 1.0% in monotherapy and no difference in visual acuity if combined with ketorolac 0.4% (corticosteroid vs corticosteroid plus NSAID). Several studies have been trying to show the effectiveness of prophylactic treatment with topical nonsteroidal antiinflammatory drugs in preventing CME. In fact, there are statistically significant differences when taking into consideration a decrease in macular thickness measurements and signs of possible edema in OCT. However, the main issue is to give those differences clinical significance, since most patients don’t develop an edema with clinical repercussion, that is, they don’t suffer low visual acuity because of the disease. Changes to the blood-retinal barrier occur in almost every operated patient, with an increase in retinal thickness according to OCT in over 40% of all patients. Most patients don’t suffer from decreased visual acuity and there is no statistical difference with prophylactic treatment when comparing different drugs. Even when theoretically more sensitive measures are considered, other than visual acuity, such as sensitivity to contrast, there are no statistically significant differences with prophylactic treatment, although a smaller increase in macular thickness and smaller loss of sensitivity to contrast have occurred. The use of NSAIDs with the usual postoperative corticosteroid treatment worked better in reducing CME detected by OCT when compared to just corticosteroids. Both topical treatment with NSAIDs and with corticosteroids seem to increase the rate of CME improvement compared to the untreated patients group. The combination of both drugs seem to have a better effect than each one by itself, both in rate of improvement and in gain of vision and contrast sensitivity. NSAIDs act by inhibiting cyclooxygenases 1 and 2, while corticosteroids inhibit COX 2 (lipoxygenases, thereby boosting their effect, so they can be combined). In general, no difference in visual acuity were observed with each class used individually or combined. The most commonly used corticosteroids for CME treatment and prevention are: prednisolone (topical), dexamethasone (topical and intravitreal implant), fluorometholone (topical) and triamcinolone (intravitreal). The most commonly used topical NSAIDs are diclofenac, ketorolac tromethamine, bromfenac, flurbiprofen, indomethacin and nepafenac. Betamethasone was used as sub-Tenon injection for treating chronic CME. An alternative reported for chronic cases is the long-acting intravitreal dexamethasone implant. Triamcinolone administered in intravitreal injections is the main option for treating chronic cases which are not responding to the traditional treatment of topical corticosteroid combined with NSAID. The duration of topical treatment is still disputed, and it is usually prescribed from 4 to 12 weeks. Antiangiogenic agents are becoming more popular in the treatment of chronic CME, aiming to reduce vascular permeability caused by the inflammatory process. Prophylaxis must be considered especially for patients with risk factors, especially uveitis, diabetes, cardiovascular diseases venous retinal occlusions and intraoperative complications, such as posterior capsular rupture and vitreous loss. Extracapsular cataract extractions or cases where phacoemulsification was not successful should also be especially examined regarding the development of cystoid macular edema and receive prophylaxis. Another group that seems to need medical prophylaxis of cystoid edema is that of patients who take drugs for glaucoma, especially...
prostaglandin/prostamide analogues. Other drugs may be related to an increase in post-surgery edema incidence, such as phenylephrine, pilocarpine, timolol, betaaxolol and other drops which use benzalkonium chloride as a preservative. In diabetic patients, macular edema is the main cause for low visual acuity after cataract surgery. The incidence in these patients is 22% and it is correlated to lower visual acuity. An early diagnosis is important in these cases, because there is evidence that when treatment is delayed, even after treating the edema, visual acuity may not be recovered. Patients using prophylaxis have not shown a higher level of edema.

CONCLUSION

Pseudophakic cystoid macular edema is the most common complication of cataract surgery and is one of the possible causes for low visual acuity after cataract surgery. Various factors have been implicated in its development but the core mechanism is likely surgically induced anterior segment inflammation that results in the release of endogenous inflammatory mediators. Anti-inflammatory medicines, including steroids and nonsteroidal anti-inflammatory drugs, have been postulated as having a role in both the prophylaxis and treatment of PCME. In summary, treatment should be applied when there is loss of visual acuity, and evidences point to a combination of corticosteroids and topical nonsteroidal anti-inflammatory drugs as the most effective way to solve the edema maintaining the NSAID for a long period. In chronic cases and those unresponsive to usual treatment, intravitreal corticosteroid injections or antiangiogenic agents have proved useful in a significant number of reports. Finally, prophylactic use of NSAIDs is still disputed for normal patients and should be applied to patients at high risk for CME.

Conflicts of interest declaration: The authors report no conflicts of interest.

REFERENCES


