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Pseudophakic Cystoid Macular Edema

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Key Words
Cataract surgery · Cystoid macular edema · Inflammatory mediators · Management

Abstract
Cataract surgery is an efficient procedure, and is generally associated with good visual results. Nevertheless, cystoid macular edema (CME) may develop, and this can result in suboptimal postoperative vision. Many factors are considered to contribute to its development, and although the treatment options depend upon the underlying cause of CME, the usual therapeutic approach for prophylaxis and treatment of CME is directed towards blocking the inflammatory mediators. This article provides a review of possible risk factors, pathogeneses, incidence rates, and methods of diagnosis, as well as the current guidelines for managing CME.

Introduction

Cataract extraction is one of the most commonly performed surgeries. Over recent years, it has benefited from consistent innovations in instrumentation, lens design, and surgical technique that have led to improved outcomes following cataract surgery [1]. Phacoemulsification using small incisions and implantation of a foldable intraocular lens (IOL) is currently the preferred technique among cataract surgeons [2]. The procedure is efficient, and uneventful surgery is generally associated with good visual results [3–5]. Nevertheless, cystoid macular edema (CME) may develop, and this can result in suboptimal postoperative vision [6–8]. It can occur after uncomplicated surgery in patients with otherwise healthy eyes, after complicated surgery, or after surgery in patients with ocular diseases such uveitis or diabetic retinopathy [9].

CME following cataract surgery was initially reported by Irvine in 1953 and demonstrated angiographically by Gass and Norton in 1966, so it is known as the Irvine-Gass syndrome [10–12].

Angiographic CME is diagnosed in patients who are otherwise asymptomatic with respect to visual acuity, but have detectable leakage from the perifoveal capillaries on fluorescein angiography (FA). Clinical CME is diagnosed in those patients who have detectable visual impairment as well as angiographic and/or biomicroscopic findings.

The clinical diagnosis is confirmed using optical coherence tomography (OCT) and FA.

The incidence of pseudophakic CME depends on the methodology used in its detection.

The prophylactic use of non-steroidal anti-inflammatory drugs (NSAIDs) preoperatively, and the combination of steroids and NSAIDs in the postoperative period, is recommended to reduce the incidence of pseudophakic CME.

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Etiology and Risk Factors

The specific etiology of aphakic and pseudophakic macular edema is not fully understood. Many factors have been considered to contribute to its development, such as the type of cataract surgery, light toxicity, vitreomacular traction, inflammatory mediators, use of adrenergic drugs, age, vitreous loss, integrity of the posterior capsule, hypertension, and diabetes [7, 13].

The type of cataract surgery used is associated with different outcomes and complications, such as CME. The change in procedure from large-incision intracapsular cataract extraction to small-incision extracapsular phacoemulsification was associated with a clear decrease in the incidence of this complication [7, 13–18]. This has been explained by less blood-aqueous barrier damage after phacoemulsification with an intact continuous curvilinear capsulorhexis than after extracapsular cataract extraction [19, 20].

Although microscope light toxicity has been indicated to be a possible contributor to CME, a prospective randomized study did not support this finding, and showed no statistically significant difference in the rate of angiographic CME from using a pupillary light occluder [21]. However, IOLs that filter UV light may reduce the rate of angiographic CME [22].

The age of the patients is another factor that needs to be considered. Some authors have indicated a positive correlation with age, demonstrating an increased incidence of CME in older patients [7, 23].

Changes occurring in the vitreous body during surgery are another pathogenic mechanism that has been proposed as a cause of CME development. Although CME can occur after uneventful cataract surgery, certain surgical complications raise the risk of CME. Rupture of the posterior capsule as well as secondary capsulotomy (including YAG laser capsulotomy) are associated with a higher rate of CME [24]. Vitreous loss increases the prevalence of CME by 10–20% [7, 25, 26]. Different studies have confirmed that the rate of clinical CME associated with vitreous loss is higher compared to cases without this complication after either extracapsular cataract extraction or phacoemulsification [25, 27–29]. The lower rate of CME occurring when there is vitreous loss during phacoemulsification has also been explained by the small wound construction and greater stability in this type of surgery compared with large-incision cataract surgery [17, 30–32]. Vitreous to the wound prolongs CME, and can be associated with a poorer prognosis [26]. Iris incarceration, an additional risk factor for CME, may have a more important association with poor vision in patients with chronic postsurgical CME than with other intraoperative complications [24, 33]. Retained lens fragments, even when they are removed by pars plana vitrectomy, are another complication associated with an increased rate of CME and more severe visual loss, in eyes with a sulcus fixated posterior chamber IOL, anterior chamber IOL, or aphakic eyes [34–37]. Retained lens fragments cause inflammation that is often severe, and these eyes have longer cataract surgery times than eyes with uneventful cataract extraction. Prolonged exposure to light from the operating microscope during the initial surgery combined with possible pars plana vitrectomy, as a second surgery, may also contribute to a higher incidence of CME [38, 39].

There are multiple reports about the association of CME after cataract surgery with the topical use of latanoprost, an ocular hypotensive lipid that is a prostaglandin analogue agent [40–43]. Other similar agents (unoprostone, travoprost and bimatoprost) were also associated with an increased incidence of CME [44]. The explanation of the increased incidence of CME associated with the prostaglandin analogues is based on the associated increase in blood-aqueous barrier disruption and inflammatory activity. Considering this possibility, it is recommended to avoid or discontinue this medication and substitute it for another type of hypotensive drug before surgery.

In diabetic patients, CME shows an increase risk, especially in patients with pre-existing diabetic retinopathy [45]. The incidence of CME in diabetic patients, even in the absence of diabetic retinopathy, is higher than in patients without this pathology [46]. Although the frequency of this problem has decreased with the widespread use of smaller incisions and phacoemulsification, it remains an important issue to consider [47]. The poor visual acuity after cataract surgery in these patients due to macular edema is common, and the two clinical forms (diabetic macular edema and edema caused by Irvine-Gass syndrome) probably co-exist [45, 48, 49]. These are difficult to differentiate, although some authors have suggested that if there is postoperative hyperfluorescence of the optic disc in the angiograms, it probably corresponds to a CME which would be likely to resolve spontaneously [50]. It is very important to take into consideration that if the patient has already some degree of macular edema when the cataract surgery is considered, it should be treated before the surgery and – in cases when this is not possible – intravitreal anti-inflammatory medication at the surgical time may be used.

Certain patients appear to have a higher risk of CME after cataract surgery. Patients with uveitis frequently develop CME, and it is the most common reason for poor

outcomes of cataract surgery in these patients [51]. After cataract surgery in patients with juvenile rheumatoid arthritis or pars planitis, the occurrence of CME can reach an incidence of about 50% [52]. Foster et al. [53] reported similar incidences in a retrospective study with uveitis patients. Other studies have reported lower incidences of CME. It is important to note that there is a wide variation in severity of uveitis, and surgeons should consider these patients at risk of postoperative CME. Taking this into account, it is imperative to control preoperative inflammation and introduce postoperative medication according the expected risk.

In conclusion, the most frequent risk factors associated with pseudophakic CME are iris trauma, rupture of posterior capsule, vitreous loss or incarceration, dislocated IOL, use of iris fixed lenses, active uveitis, and diabetes.

Pathogenesis

The pathogenesis of CME following cataract surgery remains uncertain, but clinical observations and experimental studies indicate that the pathophysiology of this postoperative problem may be multifactorial [26, 39]. Among the factors of potential clinical importance are vitreous traction [10, 54], functional disturbance of the blood-retinal barrier (BRB) [13, 55–57], and inflammation mediated by prostaglandins [7, 39, 58–62]. Most investigators consider inflammation as the major etiologic factor in the development of CME following cataract surgery. It is noteworthy that inflammation is directly associated with a breakdown of the BRB. It is probable that after surgery the inflammation mediators (prostaglandins, cytokines, and other vascular permeability factors) are released from the anterior segment of the eye and diffuse to the vitreous cavity and retina, stimulating the breakdown of the BRB and subsequent leakage of fluids across the retinal vessel wall and through the retinal pigment epithelium (RPE) into perifoveal retinal tissues resulting in macular edema [13, 63, 64]. Surgical manipulation, which happens during the cataract surgery, always causes trauma to the iris. It is known that the iris is a metabolically active tissue that releases inflammatory mediators when traumatized. After surgery, the physiological healing process is sufficient to slowly, but progressively, suppress the inflammation [65]. In about 90% of patients with macular edema following cataract surgery, a spontaneous resolution of the edema and a recovery of visual acuity can be observed. In specific situations, an excessive leakage occurs, which can lead to a severe and irreversible impairment of visual acuity. The different degrees of leakage explain the higher incidence of angiographically detectable CME compared to clinically identified CME [66].

The inflammatory mediators probably play the essential initiating role in the development of inflammatory CME, but the exact factors and events responsible for further CME development and its chronicity have not yet been clearly identified.

Incidence

Though the rate of CME has been declining with decreasing surgical incision and the use of microsurgical instrumentation, the high volume of cataract surgeries performed each year makes CME a common cause of poor vision in pseudophakic patients [32].

Determining the overall incidence of CME has been difficult because of variations in the patient populations evaluated (with varying risk factors) and the use of different methods for evaluating macular thickening. Another factor that contributes to the uncertain incidence is the use of different prophylactic medications before and after cataract surgery. There are multiple reports comparing the incidence of clinical and angiographic CME under specific anti-inflammatory drugs [67–69]. The multiple reports and reviews that mention or discuss the incidence of CME show different numbers and the explanations are, in certain cases, unclear [26, 70]. However, it is important to recognize the many variables involved and the difficulty in identifying their potential impact on the interpretation of results from therapeutic trials that evaluated potential treatments for CME.

The true current incidence of clinical CME using modern techniques appears to be very low in uncomplicated cases. It is likely to be in the range of 0.2–2%, and the rate of angiographic CME is at least ten-fold higher in magnitude [26, 32, 71]. These numbers increase if another large-incision technique is required, instead of small-incision phacoemulsification with implantation of a foldable IOL; they also increase if we have a complicated surgery with iris trauma, or capsule rupture with vitreous loss, or in patients at high risk (such as those with uveitis or diabetes).

Diagnosis

The diagnosis of CME can generally be made on clinical examination with evidence of perifoveal cystic spaces, and has traditionally been confirmed with use of FA

to document the classic petaloid pattern of leakage induced by inflammatory mediators that lead to breakdown of the BRB. Today, the most definite evidence is obtained from OCT examination.

Signs and symptoms of clinically significant CME typically develop 4–12 weeks after surgery and reach a peak at 4–6 weeks postoperatively. The patient may complain of impaired vision after an initial period of improved vision [24]. Generally, this responds to treatment with topical anti-inflammatory medications and usually resolves within 6 months. However, some cases respond poorly to conservative treatment, persist for more than 6 months, and may develop permanent visual loss. Although the incidence of chronic CME is much less frequent, being reported at 1–2% of uncomplicated cases and about 8% after complicated cataract surgery, the associated vision loss makes it a serious complication.

In ophthalmoscopy and biomicroscopy, the loss of foveal depression is the most frequent sign of CME. Intraretinal cystoid spaces can be detected and the perifoveal area can appear with a yellowish coloration [7, 24, 32]. A swelling of the optic nerve head can be detectable [26]. In cases of chronic CME, the cystoid spaces fuse to foveal cysts.

Angiographic CME is diagnosed in patients who are otherwise asymptomatic with respect to visual acuity, but have detectable leakage from perifoveal capillaries on FA demonstrated by hyperfluorescence in the central macula and optic disc. Clinical CME is diagnosed in those patients who have detectable visual impairment as well as angiographic and/or biomicroscopic findings [32, 72].

In the early phase of the FA, capillary dilatation and leakage from small perifoveal capillaries are visible. In later phases, pooling in the outer plexiform layer results in the classic perifoveal 'petaloid' staining pattern. Another common sign is late leakage and staining of the optic nerve due to capillary leakage [73]. In severe CME, the cystoid spaces may have a 'honeycomb' appearance in FA, corresponding to large cystoid spaces, extending outside the immediate perifoveal region [24]. Vitreous fluorometry, a more sensitive technique for measuring alterations in the BRB using fluorescein, shows an even higher incidence of alterations in the period immediately after cataract surgery [55]. The retinal leakage analyzer is a methodology that can be used to objectively measure the disruption of the blood-retinal barrier, leading to a quantitative evaluation of the macular edema [74].

With OCT, it is possible to observe the cystic spaces in the outer nuclear layer of the central macula and, in correlation with histological findings, measure the edema which should correspond to the value of the observed retinal thickening [75–77]. The foveal thickness can increase significantly, and it correlates moderately with the decrease in visual acuity, but clearly better than the correlation between FA and visual acuity.

Although the FA has been considered the diagnostic gold standard for pseudophakic CME, OCT is now the method of choice, being a non-invasive technique to evaluate and follow CME after cataract surgery [78]. An additional advantage of the use of OCT is that the thickening of macular area effectively measures the edema, and therefore correlates better with vision than the angiogram grading [26].

Classification

Angiographic CME is defined as the presence of fluorescein leakage on FA. It is mostly asymptomatic. A decrease in visual acuity does not correlate with an extension of leakage. Clinically significant CME presents with decreased vision, and is generally diagnosed by biomicroscopy and OCT.

Usually the CME appears within 4 months of surgery, and is designed as acute. If the onset occurs after more than 4 months postoperatively, it is designed late-onset CME.

The CME is classified as chronic if it lasts more than 6 months.

Management

Angiographic CME after cataract surgery is not necessarily associated with poor visual outcome. Usually it resolves spontaneously and only about 1–3% of cases persist, and this corresponds to clinical CME with persistent symptoms [79].

It is now accepted that in cataract surgery it is important to perform a therapeutic intervention both for prophylaxis and for treatment of CME based on the existing knowledge of its pathogenesis. Many of the multiple studies performed to test the efficacy of different drugs in pseudophakic CME have been poorly designed. Therefore, the results are not consistent and controversy persists. However, it is now widely accepted that it is important to introduce anti-inflammatory drugs not only to treat but also specifically to prevent the development of CME after cataract surgery [80, 81].

Although the treatment options depend on the underlying cause of CME, the usual therapeutic approach for

the prophylaxis and treatment of CME is directed towards blocking the inflammatory mediators, mainly the prostaglandins in the anterior segment of the eye, using topical steroids and NSAIDs.

Topical NSAIDs have demonstrated effectiveness in preventing both angiographic and clinical CME [68]. There are multiple reports concerning the use of different NSAIDs in the prevention and treatment of CME. In general, studies have proven the effectiveness of use of this type of medication, and without clear statistical differences between the different NSAIDs.

Corticosteroids are effective, but they can cause an increase in intraocular pressure in a small percentage of patients. Usually the medical treatment of uncomplicated cases can first include NSAIDs with, in some cases, the addition of topical steroids. Clinical evidence suggests that the combined use of NSAIDs and steroids is synergistic [82, 83].

In patients with evidence of anterior segment inflammation or those with chronic CME following posterior capsule trauma, steroids have been shown to be effective, and a stepwise plan may be undertaken starting with topical administration, followed by local injection, reserving high-dose intra-vitreous administration for severe refractory cases. This can reduce macular edema and improve vision in eyes with CME that persists or recurs despite previous medical treatment [84–86]. However, CME may recur in some cases, even after more than one intravitreal injection of triamcinolone acetonide.

A carbonic anhydrase inhibitor (acetazolamide) may help reduce the edematous component. These have the ability to stimulate the RPE to pump excess fluid out of the macula. Furthermore, carbonic anhydrase inhibitors induce acidification of the subretinal space, and thereby increase fluid resorption from the retina through the RPE into the choroid [24, 87]. There are some reports documenting the positive effect of acetazolamide in post-surgical CME [88].

The use of antiangiogenic agents has also been proposed as an alternative therapeutic approach in some cases of refractory CME. VEGF, a potent inducer of alterations in the BRB, may be increased in postoperative CME. However, bevacizumab, a monoclonal antibody against all isoforms of VEGF, which has been used to treat some neovascular diseases, was used in patients with postoperative CME without positive effects [89].

Vitreolysis using the Nd:YAG laser has shown positive effects in cases of vitreous incarceration in the cataract incision wound [90].

Surgical treatment, namely vitrectomy, is indicated in some specific cases of chronic CME and appears to be effective. The rationale for performing vitrectomy in CME following surgery includes the removal of vitreous adhesions and inflammatory mediators and improved access of topical medication to the posterior pole.

The current guidelines for managing post-cataract surgery inflammation state that the prevention of inflammation should be the main goal, with good patient selection, correct eye/patient preparation, taking special care during surgery not to cause iris trauma, appropriate resolution of intraoperative complications, and timely treatment of postoperative inflammation [91].

It should be noted that diabetic patients with pre-surgical macular edema have a higher risk of worsening their macular edema after cataract surgery. In these patients, it is recommended to first treat the macular edema and only perform the surgery afterwards. In these cases, the use of intravitreal triamcinolone acetonide (4 mg) injected at the end of cataract surgery is indicated.

Conclusions/Recommendations for Managing Pseudophakic CME

- First, it is very important to perform a correct preoperative evaluation of the patient. Patients can be divided into normal and high-risk cataract patients.
- If s/he is a high-risk patient, the potential for improvement or correction should be considered, and, if indicated, medication should be introduced and the therapeutic schema adapted.
- If s/he is a normal patient, it is recommended (as prophylaxis) to administer topical NSAIDs during the first month in combination with topical steroids, using decreasing doses during the first 2 weeks.
- If there is a recognized CME, first the topical NSAIDs and steroids should be re-introduced for 1 month. After this, visual acuity should be evaluated and an OCT should be performed to estimate any possible improvement in the CME.
- If the CME has not improved, the introduction of acetazolamide (for 1 month or more) should be considered, or, as an alternative, a periocular corticosteroid or intravitreal triamcinolone.
- If there is vitreous incarceration or a persistent inflammatory reaction, surgery it (vitrectomy) should be considered.

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