

Prostaglandin Analogs and Cataract Surgery

What is the proper perioperative management of cataract surgery patients taking glaucoma medications?

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Given the high prevalence of ocular hypertension and glaucoma in patients undergoing cataract extraction, all cataract surgeons face the question of whether it is safe to use prostaglandin analogs during the perioperative period. The primary concern about this class of drugs in these patients is the possible association between their use and cystoid macular edema (CME). The variability of criteria for defining significant CME¹ along with a lack of understanding as to what causes the condition in some patients but not others makes it difficult to establish a causal association with putative risk factors. This article assesses and summarizes the literature pertaining to such causality and shares our recommendations on how to approach the patient requiring cataract surgery who is receiving prostaglandin therapy.

CASE REPORTS

Several published case reports have demonstrated a temporal association between the use of prostaglandin analogs and CME in pseudophakic patients.²⁻⁷ Some have reported the impressive resolution of CME and prompt visual improvement upon the cessation of prostaglandin therapy in conjunction with the administration of topical steroidal and nonsteroidal anti-inflammatory therapy.^{3,4,6-11} Other case reports have been less convincing due to methodological limitations. Case reports and series are clearly not substitutes for well-designed, adequately powered, randomized clinical trials, particularly when the potential impact of study findings on clinical care is significant.

HOW COMMON IS CME FOLLOWING CATARACT SURGERY?

The prevalence of CME after cataract surgery largely depends on how one defines the condition. The term *angiographic CME* refers to the condition as defined and graded by a spectrum of findings on fluorescein angiography.¹ The reported prevalence of CME based upon fluorescein angiography was as high as 30% following extracapsular cataract extraction in one report.¹² The incidence of *clinical CME* (defined ophthalmoscopically by the detection of abnormal cystoid spaces in the macula), however, is much lower. A third criterion for CME relates to the diminution of vision associated with angiographically verified CME. Labeled by some as *clinically significant CME*,¹ its prevalence is reported at between 1% and 5%,^{13,14} the variation largely due to preoperative risk factors in the study populations.

The variance in definitions of CME is particularly important when reviewing the literature. The higher rates of angiographic CME relative to clinically significant CME make the former a more attractive endpoint for study design, given that fewer patients are needed to establish causality. Because cataract surgeons hope to satisfy their patients, however, the incidence of clinically significant CME is more relevant to their practice. Strict cause-and-effect relationships are difficult to establish in many areas of medicine, and a rudimentary understanding of a disease process coupled with a less-than-optimal concordance between structural and functional macular changes in CME patients makes this a difficult topic for study.

WHAT CAUSES CME?

Several modulators have been implicated in the causation of CME. These include complement, platelet-activating factor, cytokines, interleukin-6, lysosomal enzymes, vascular endothelial growth factor, and, most notably, products of the arachadonic acid cascade such as prostaglandins (PGE₂, etc.).¹⁵ These mediators are thought to cause the breakdown of the blood-aqueous barrier and ultimately the blood-retina barrier, which both contribute to the development of CME. Pharmacokinetic research has further demonstrated, through the use of radiolabeled prostaglandin esters, that the level of topical medications in the retina and choroid is potentially high enough to affect retinal physiology.¹⁵ A causal relationship between such medications and CME, however, remains difficult to establish.

Hypothetically, the initial insult leading to CME in pseudophakic patients is operative irritation of uveal tissue along with the release of lens epithelial cells.¹⁶ The fact that the prostaglandin analog class of glaucoma medications is thought to work primarily through binding to the prostaglandin F receptor has led many ophthalmologists to postulate that this must be the mechanism of postoperative CME in patients using these medications. Surprisingly, however, one study on the subject revealed that it was not the prostaglandin but rather the drug's preservative that was linked to postoperative CME.¹⁷ The issue of causality with glaucoma medications is clearly more complex than initially theorized.

WHO IS AT HIGH RISK?

Although it is simpler to have a universal preferred practice pattern for patients undergoing cataract surgery, the data indicate that a complex algorithm may be more appropriate for identifying individuals who may develop CME while using glaucoma medications during the period following cataract surgery. Multiple studies have indicated that patients at high risk for CME include those with a history of retinal vein occlusion, diabetes, vitreous loss, uveitis, vitreomacular traction, an epiretinal membrane, aphakia, and an absent posterior capsule (postcapsulotomy or via an intraoperative complication).¹⁴ Given ophthalmologists' knowledge of the pathogenesis of CME and its relationship to increased intraretinal vascular permeability, the list of disease entities linked to this condition is not surprising. Even in such high-risk groups, however, the overall incidence of postoperative clinically significant CME following cataract surgery is generally no more than 5%.¹⁴

Notwithstanding the lack of proof that the preoperative use of prostaglandins causes CME, it makes sense to consider stopping the agents sometime prior to cataract surgery to minimize the potential risk. How long before the

procedure their use should cease and when they should be resumed postoperatively, however, remain widely debated questions. The vast majority of patients undergoing cataract surgery do not have these comorbidities, and the case for preoperatively stopping prostaglandins for a period of time is difficult to justify, particularly because patients are presumably using these agents to lower their IOP to a safe level. The practical question in this debate is not necessarily whether or not prostaglandin analogs and their associated preservatives can lead to CME. Rather, one must ask, does the risk of poorly controlled IOP outweigh the benefits of avoiding a relatively uncommon phenomenon that has not been causally linked to a particular class of drugs?

A survey of the Royal College of Ophthalmologists conducted by Ahad and McKee demonstrated that approximately 60% of the doctors did not stop treatment with prostaglandin analogs for uneventful cataract surgery. Of those who discontinued the drugs, approximately half did so routinely, whereas the other half did so only in high-risk patients. A majority of physicians who stopped prostaglandins did so less than 1 week prior to surgery, and most restarted therapy 30 to 60 days postoperatively, if needed.¹⁸

THE POSTOPERATIVE USE OF PROSTAGLANDINS

Cataract surgery is arguably the most commonly performed procedure for lowering IOP. Although what happens to the IOP varies widely among patients following phacoemulsification and the implantation of an IOL, a drop in the average IOP has occurred after surgery in almost every examined study population.¹⁹⁻²² Modern cataract surgery may decrease the need for some or all of the glaucoma medications that a patient has been using. Ophthalmologists therefore may stop prostaglandins at the time of cataract surgery in virtually all patients.

In fact, prostaglandins are actually less than ideal for lowering IOP during the immediate postoperative period. Faster-acting drugs such as alpha adrenergic agonists, beta-blockers, and topical and systemic carbonic anhydrase inhibitors (CAIs)—all of which decrease the production of aqueous humor—are generally preferable. Prostaglandins mediate inflammation, which raises a concern about their use during the postoperative period when ocular inflammation is already present. Although evidence that topical prostaglandins cause or exacerbate inflammation is clearly not overwhelming, most ophthalmologists would agree that using these agents in the early postoperative period is not optimal. A majority of practitioners would also agree that, when necessary during the first few weeks following cataract surgery, patients should use prostaglandins in conjunction with topical nonsteroidal anti-inflammatory agents to minimize the potential risks of both CME and

exacerbated postoperative inflammation. The use of topical steroids is, of course, also desirable in such situations.

SUMMARY AND RECOMMENDATIONS

There is no Oxford Level I highest-quality evidence demonstrating harm from the use of prostaglandin analogs prior to or after cataract surgery. The association between these drugs and CME or ocular inflammation remains controversial. Regarding CME, the impact of preservatives also found in other topical glaucoma medications may be more significant than the active components of prostaglandins. Nonetheless, common sense dictates discontinuing prostaglandins perioperatively in patients with preexisting CME or risk factors for developing the condition as well as individuals with other macular diseases for whom the occurrence of CME may have devastating consequences. Similarly, surgeons may wish to avoid prostaglandins in patients undergoing cataract surgery who have a history of ocular inflammatory disease.

We recommend stopping prostaglandins 1 week prior to surgery in high-risk patients when their IOP can be controlled by other agents such as oral CAs or when their glaucoma is not severe enough to place them at significant risk of ultimate visual deterioration. The 1-week preoperative stopping date is completely arbitrary, as it remains unknown how long the adverse effects (if any) of prostaglandins last following the drugs' discontinuation.

Prostaglandins are our last choice for lowering IOP during the week following cataract surgery for a variety of reasons. Postoperative IOP spikes can generally be controlled by aqueous suppressants such as alpha adrenergic agonists, beta-blockers, or topical and oral CAs, none of which is a likely mediator of inflammation. If prostaglandins are necessary for controlling IOP in the first 2 to 4 weeks following cataract surgery when ocular inflammation is present, we recommend using adjunctive topical nonsteroidal anti-inflammatory agents, which have not been shown to affect the IOP-lowering response.^{21,23,24} Prostaglandins, if needed, are routinely resumed at approximately 1 month following cataract surgery, when they sometimes replace aqueous suppressing therapy.

Cataract surgery provides an opportunity to stop glaucoma medications. In our experience, a substantial proportion of patients who required prostaglandin therapy prior to cataract surgery will not need any glaucoma medications in the long-term postoperative period. When pseudophakic patients require long-term IOP-lowering therapy, however, prostaglandins remain our preferred first-line agents after the first postoperative month. We shorten or extend this timing if patients recover faster or slower than average, respectively, with regard to ocular inflammation after cataract surgery. ■

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