Prevention of CME After Cataract Surgery

Investigators of the ESCRS PREMED study hope to establish evidence-based clinical guidelines.

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Cystoid macular edema (CME) is one of the most common causes of vision loss after cataract surgery. Its pathogenesis is likely multifactorial, but inflammation caused by surgical manipulations appears to be a major cause (Figure 1).1,2 Prostaglandins interact with and amplify other inflammatory mediators and induce vascular endothelial growth factor (VEGF) production, causing vasodilation and disruption of the blood-retina barrier and leading to increased vascular permeability. As a result, transudate accumulates in the retina’s outer plexiform and inner nuclear layers, and CME develops.3,4

Between 4% and 20% of healthy eyes develop CME after cataract surgery,5-7 but most patients experience little to no reduction in visual acuity. The estimated incidence of clinically significant macular edema (CSME) is between 0% and 5.8%.8-11 CSME is most likely to present in patients with diabetes; up to 56% of nonproliferative diabetic retinopathy patients without diabetic macular edema at baseline develop CSME after cataract surgery.5,11-13 Given that 16% of patients undergoing cataract surgery have diabetes, this represents a significant part of CME cases.14-16

Investigators have tried various strategies to address the problem of CME after cataract surgery, but there remains a lack of well-designed randomized controlled trials to investigate the efficacy of these treatments.4 Due to the lack of well-designed trials and because of the large variety of treatments in use in clinical practice, we recently initiated a study to establish definitive evidence-based recommendations to prevent CME after cataract surgery in patients with and without diabetes.

The European Society of Cataract and Refractive Surgeons (ESCRS) Prevention of Macular Edema After Cataract Surgery (PREMED) study is an international multicenter study funded by the ESCRs. The study is designed to compare the efficacy of several pre-, intra-, and postoperative treatments for the prevention of CME after cataract surgery. Enrollment began in July 2013.

PATIENTS WITHOUT DIABETES

Treatment protocol. Patients without diabetes will be randomized to receive one of the following treatments:

- Bromfenac 0.09% eye drops twice daily, starting 2 days before surgery and continuing for 2 weeks postoperatively;
- Dexamethasone 0.1% eye drops four times daily, starting 2 days before surgery and continuing four times daily during the first postoperative week and one drop less per day each following week; or
- A combination of bromfenac and dexamethasone eye drops in the aforementioned dosages.

Available evidence. Corticosteroids are traditionally used to prevent ocular inflammation, and they have also been shown to be an effective treatment for CME after cataract surgery. Whereas other antiinflammatory drugs inhibit the action of only a specific inflammatory mediator, corticosteroids inhibit the production of various inflammatory cytokines.17

Several topical NSAIDs are registered for the treatment and prevention of postoperative inflammation and are commonly used to prevent CME after cataract surgery. According to the literature,18-20 bromfenac has several benefits over other topical NSAIDs. Its chemical structure is similar to amfenac, except for an additional bromine atom that facilitates absorption across the cornea and penetration into ocular tissues. This additional atom also extends the duration of antiinflammatory activity and enhances the molecule’s inhibitory effect on cyclooxygenase (COX)-2.18-20 Cable et al12 compared the effects of bromfenac and nepafenac after cataract surgery and found significantly better postoperative BCVA and less increase in macular volume and retinal thickness in the bromfenac group than in the nepafenac group.

In general, NSAIDs more effectively prevent CME after cataract surgery compared with corticosteroids. In a comparison of bromfenac, dexamethasone, and fluorometholone treatments in a population of 240 patients without...
diabetes undergoing cataract surgery, Wang et al\textsuperscript{21} found that foveal thickness was lower in the bromfenac group than in the corticosteroid groups for up to 2 months postoperatively. CME was reported in 0.0%, 7.0%, and 9.8% of patients in the bromfenac, fluorometholone, and dexamethasone treatment groups, respectively. Likewise, Endo et al\textsuperscript{22} investigated the efficacy of bromfenac versus corticosteroids in 62 patients with diabetes who had no signs of CME preoperatively. In patients with nonproliferative diabetic retinopathy, there was significantly lower perifoveal thickness in the bromfenac group than in the corticosteroid group at 4 and 6 weeks postoperatively.

Other studies suggest that a combination of topical corticosteroids and NSAIDs is more effective than either agent alone. Reports indicate that patients have had better visual acuity, lower macular volume, lower central subfield mean thickness, and lower incidence of CME after combination treatment.\textsuperscript{23-27}

**PATIENTS WITH DIABETES**

**Treatment protocol.** Patients with diabetes will be randomized to receive one of the following treatments:

- Bromfenac 0.09% and dexamethasone 0.1% eye drops in the aforementioned doses;
- Bromfenac and dexamethasone eye drops as above and a subconjunctival injection of 40 mg preservative-free triamcinolone acetonide (TA);
- Bromfenac and dexamethasone eye drops as above and an intravitreal injection of 1.25 mg bevacizumab; or
- Bromfenac and dexamethasone eye drops as above, a subconjunctival injection of TA, and an intravitreal injection of bevacizumab.

**Available evidence.** Surgical manipulations cause a release of prostaglandins from, at least in part, uveal tissues in the anterior segment.\textsuperscript{1} In order to prevent or reduce postoperative inflammation and macular edema, this release of prostaglandins must be inhibited in the anterior segment. Although lower concentrations of TA reach the retina after subconjunctival injection, higher levels reach the anterior segment via diffusion through puncture sites in the conjunctiva and through the tear film and cornea.\textsuperscript{28,29} In a recent randomized clinical trial, subconjunctival corticosteroid injection and topical corticosteroid application showed comparable results in preventing postoperative inflammation and CME after cataract surgery in patients without diabetes.\textsuperscript{30}

As mentioned previously, the pathogenesis of CME is related to changes in concentrations of inflammatory mediators and angiogenic factors such as VEGF. Studies have shown that, before cataract surgery, a high aqueous level of VEGF is a significant predictor of the occurrence of postoperative CME.\textsuperscript{31,32} As a VEGF inhibitor, bevacizumab is thought to diminish breakdown of the blood-retina barrier and accumulation of fluid in the retina after cataract surgery. Although several studies have investigated the efficacy of this drug in preventing retinal thickening after cataract surgery, most are small and not well designed.\textsuperscript{33} Previous studies investigating 26 to 68 eyes with preoperative diabetic macular edema (DME) reported significant reduction in retinal thickness and macular volume after intravitreal injection of bevacizumab during cataract surgery.\textsuperscript{34-38} In 61 patients with nonproliferative diabetic retinopathy but with no signs of DME preoperatively, Fard et
al\(^{40}\) found that retinal thickness did not change at 4 weeks postoperatively in the eyes treated with bevacizumab at the end of cataract surgery. However, it had increased significantly in the control group.

**CURRENT STUDY**

The planned ESCRS PREMED study population consists of 1,050 patients without diabetes and 300 patients with diabetes mellitus who require cataract surgery in at least one eye.\(^{40}\) Twelve study centers will take part in this study: Vienna Institute for Research in Ocular Surgery (Austria), University Hospital Antwerp (Belgium), Goethe University Frankfurt am Main (Germany), Augenklinik Spreebogen Berlin (Germany), Semmelweis University Budapest (Hungary), Hospital and University of Verona (Italy), University Hospital Coimbra (Portugal), S. Fyodorov Eye Microsurgery Complex Moscow (Russia), Instituto Microcirugia Ocular Barcelona (Spain), Atrium Medical Center Heerlen (Netherlands), VU University Medical Center Amsterdam (Netherlands), and the University Eye Clinic Maastricht (Netherlands). The final results of the ESCRS PREMED study will be available in 2015.

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