

Ophthalmic Technology Assessment

Topical Nonsteroidal Anti-inflammatory Drugs and Cataract Surgery

A Report by the American Academy of Ophthalmology

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Objective: To review the available evidence on the effectiveness of prophylactic topical nonsteroidal anti-inflammatory drugs (NSAIDs) in preventing vision loss resulting from cystoid macular edema (CME) after cataract surgery.

Methods: Literature searches of the PubMed and the Cochrane Library databases were last conducted on January 21, 2015, with no date restrictions. The searches retrieved 149 unique citations. The first author reviewed the abstracts of these articles and selected 27 articles of possible clinical relevance for full-text review. Of these 27 articles, 12 were deemed relevant to analyze in full. Two additional articles were identified from the reference list of the selected articles, and another article was identified from a national meeting. The panel methodologist assigned ratings of level of evidence to each of the selected citations.

Results: Nonsteroidal anti-inflammatory drug therapy was effective in reducing CME detected by angiography or optical coherence tomography (OCT) and may increase the speed of visual recovery after surgery when compared directly with placebo or topical corticosteroid formulations with limited intraocular penetration. However, the use of NSAIDs did not alter long-term (≥ 3 months) visual outcomes. Furthermore, there was no evidence that the benefits observed with NSAID therapy could not be obtained similarly with equivalent dosing of a corticosteroid. The reported impression that there is a pharmacologic drug synergy from the use of both an NSAID and a corticosteroid is not supported by the literature. There is no uniform method of reporting CME in the literature, which prevents accurate assessment of its incidence and response to anti-inflammatory therapies.

Conclusions: Cystoid macular edema after cataract surgery has a tendency to resolve spontaneously. There is a lack of level I evidence that supports the long-term benefit of NSAID therapy to prevent vision loss from CME at 3 months or more after cataract surgery. Although dosing of NSAIDs before surgery may hasten the speed of visual recovery in the first several weeks after cataract surgery, there is no evidence that this practice affects long-term visual outcomes. Standardized reporting of CME based on OCT may allow for more uniform quantitation of its incidence and more reliable assessment of treatment outcomes. *Ophthalmology* 2015;■:1–10 © 2015 by the American Academy of Ophthalmology.

The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to review systematically the available research for clinical efficacy, effectiveness, and safety. After review by members of the Ophthalmic Technology Assessment Committee, other Academy committees, relevant subspecialty societies, and legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements. The purpose of this assessment by the Ophthalmic Technology Assessment Committee Retina/Vitreous Panel is to evaluate the effectiveness of prophylactic topical nonsteroidal anti-inflammatory drugs

(NSAIDs) in preventing vision loss resulting from cystoid macular edema (CME) after cataract surgery.

Background

At least 1.8 million cataract surgeries are performed on Medicare patients annually in the United States (2012–2013 Medicare data as compiled and published by the American Medical Association). Development of CME after cataract surgery is the most common cause of visual impairment. Cystoid macular edema can be classified as clinical (bio-microscopic-observed retinal thickening in combination with visual impairment), angiographic (leakage detected on

fluorescein angiography), and more recently on the basis of optical coherence tomography (OCT) results (OCT-based intraretinal fluid with or without subretinal fluid). Incidence rates of CME vary substantially throughout the literature, depending on which definition is used and the type of patients who are studied. For example, CME occurs at higher frequencies among patients with uveitis or diabetes.^{1,2} Recent studies have reported incidence rates after uncomplicated modern small-incision cataract surgery in healthy individuals (without diabetes or uveitis) as high as 9% to 19% using fluorescein angiography, but visually important CME is reported at much lower rates in the range of 1% to 4%.³ Although CME can be treated, its development increases the cost of cataract surgery by approximately 50% (additional cost in 2014, \$1092), and chronic CME can result in permanent visual impairment.⁴

Although the exact pathogenesis of CME remains to be elucidated, disruption of the blood-retinal barrier resulting from inflammation after cataract surgery may play a causative role. It has been hypothesized that release of prostaglandins and other inflammatory mediators increases permeability of perifoveal capillaries, resulting in accumulation of fluid and cystoid changes in the retinal layers.⁵ Consequently, corticosteroid treatment has been administered commonly for its anti-inflammatory effects.⁶ Nonsteroidal anti-inflammatory drugs often are used in conjunction with topical corticosteroids and less commonly as a substitute. Some surgeons preferentially start an NSAID before surgery.

Nonsteroidal anti-inflammatory drugs specifically inhibit cyclooxygenase enzyme, and thereby the synthesis of all downstream proinflammatory prostaglandins.^{5,6} The anti-inflammatory properties of NSAIDs largely result from this mechanism. Corticosteroids, however, inhibit prostaglandins and leukotrienes, and they downregulate several other inflammatory-mediated events (e.g., epithelial adhesion, emigration, chemotaxis, phagocytosis). Consequently, corticosteroids possess far broader anti-inflammatory properties than NSAIDs. Although NSAIDs are not associated with elevated intraocular pressure and provide a distinct clinical advantage over corticosteroids in this regard, increases in intraocular pressure with short-term use of corticosteroids in the setting of cataract surgery typically are mild and self-limited.

There are no United States Food and Drug Administration (FDA)-approved treatments for the prevention of CME after cataract surgery, but an extensive meta-analysis of the world literature in 1998 concluded that treatment with NSAIDs is beneficial.⁷ A subsequent major review of the literature on this topic in 2010 reported similar findings, but emphasized the paucity of well-designed studies and the lack of evidence of long-term benefit in preventing vision loss from CME.⁸ A recent meta-analysis published in 2014 reported that topical NSAIDs are more effective than topical corticosteroids in preventing CME after cataract surgery and advocated their use after routine surgery.⁹ However, this meta-analysis may be limited by publication bias (the tendency to publish studies with positive findings instead of those studies showing little or no effect).

In particular, because many cases of CME are mild and resolve spontaneously, it remains unknown whether

prophylactic NSAID treatment improves long-term visual outcomes. It also remains unclear whether prophylactic treatment prevents the onset of chronic CME (present >6 months after surgery) or in some way decreases its severity. Accurately estimating the therapeutic benefit of NSAIDs is also challenging, because most studies involve concomitant corticosteroid use. Several reports in the literature claim that use of an NSAID and a corticosteroid is synergistic.^{9–11}

Despite the growing popularity of adding a topical NSAID to a topical corticosteroid to prevent CME after cataract surgery, there continues to be uncertainty about the benefits of NSAID preparations as a result of conflicting results in the literature, methodologic limitations of published studies, and potential conflicts of interest among proponents of this practice. For example, many of the studies compared topical NSAIDs with fluorometholone 0.1%, which has limited intraocular penetration and therefore may approximate the effectiveness of NSAIDs as compared with placebo. The benefits of NSAID treatment also should be weighed against added cost and the potential for adverse effects. For example, NSAID use has been associated with keratopathy, corneal melts, and rarely, severe allergic reactions.^{8,10} Therefore, the panel systematically reviewed the literature to determine the level of evidence supporting the effectiveness of NSAIDs, alone or in combination with corticosteroids, in preventing vision loss resulting from CME after cataract surgery.

Description of the Intervention

Several NSAID formulations currently are available in the United States: flurbiprofen sodium 0.03%, diclofenac sodium 0.10%, ketorolac tromethamine 0.40% and 0.50%, preservative-free ketorolac tromethamine 0.45%, bromfenac sodium 0.07% and 0.09%, and nepafenac suspension 0.10% and 0.30%. Suprofen 1.0%, an older formulation, is no longer commercially available. Other topical formulations, such as indomethacin 1.0%, are available outside the United States. Most topical formulations are FDA approved to prevent inflammation after cataract surgery. Other FDA-approved indications for specific topical formulations include the prevention of surgical miosis (flurbiprofen 0.03%), treatment of seasonal allergic conjunctivitis (ketorolac 0.50%), and reduction of ocular discomfort after refractive surgery (diclofenac 0.10%, ketorolac 0.40%). Nonsteroidal anti-inflammatory drugs are not FDA approved for the prevention of CME, for the treatment of CME, or for treatment in excess of 14 days, but off-label use for these indications and for longer periods are common.

Resource Requirements

Most treatment regimens consist of a 4- to 6-week course, which may begin several days before surgery. The average wholesale price of a 30-day supply can range from \$70 to \$130 and may add as much as \$180 to the cost of cataract surgery. Because nearly 3 million cataract surgeries are performed yearly in the United States, routine use of NSAIDs

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