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 ($\geq$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;122:2159-2168 © 2015 by the American Academy of Ophthalmology.*

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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 (biomicroscopic-observed retinal thickening in combination with visual impairment), angiographic (leakage detected on

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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

therefore could correspond to an aggregate societal cost as high as $540 million annually if provided after every surgery.

Question for Assessment

The objective of this assessment was to address the following question: Does prophylactic use of NSAIDs reduce vision loss from CME after routine cataract surgery? Specific outcomes to be assessed included (1) visual acuity at 3 months or more after surgery and (2) the incidence of CME.

Description of Evidence

Literature searches of the PubMed and the Cochrane Library databases were conducted last on January 21, 2015, with no date restrictions. The searches retrieved 149 unique citations. The search strategy used was as follows: (*macular edema* [Mesh] OR *macular edema* [tiab] OR *macular oedema* [tiab] OR *irvine gass** OR *cystoid macular** OR *cystic macular** OR *macular thicken** OR (*macular inflammation* NOT *macular degeneration*) AND (*anti-inflammatory agents, non-steroidal* [Mesh] OR *anti-inflammatory agents, non-steroidal* [*pharmacological action*] OR *nsaid* [tiab] OR *nsaids* [tiab] OR *non-steroidal anti-inflammatory agent* [tiab] or *non-steroidal anti-inflammatory agents* [tiab]) AND (*cataract extraction* [Mesh] OR *cataract extraction* [tiab] OR (*cataract* [tiab] AND *surger** [tiab]) OR *cataract removal* [tiab] OR *post-cataract* [tiab] OR *cataract* [Mesh] OR *lens implantation, intraocular* [Mesh] OR *lenses, intraocular* [Mesh]).

The first author (S.J.K.) reviewed the abstracts of these articles and selected 27 citations of possible clinical relevance for full-text review. Of these, 12 were deemed to be of sound methodologic design with a sufficient number of patients to analyze in full. Two additional articles were identified from the reference list of the selected articles, and another peer-reviewed article was identified from a national meeting (American Society of Cataract and Refractive Surgery Symposium and Congress, March 25−29, 2011, San Diego, CA). All 15 were deemed of sound methodologic design with a sufficient number of patients to analyze in full. The panel methodologist (J.E.T.) reviewed the 15 studies and assigned a level of evidence to each of the final selected articles based on a rating scale developed by the British Centre for Evidence-Based Medicine.[11] A level I rating was assigned to well-designed and well-conducted randomized clinical trials; a level II rating was assigned to well-designed case-control and cohort studies and poor-quality randomized studies; and a level III rating was assigned to case series, case reports, and poor-quality cohort and case-control studies.

Published Results

In the search of 149 citations, 12 citations of clinical studies were selected to be analyzed in full. Eleven of these 12 citations were randomized prospective studies, of which 8 were randomized controlled studies (included a placebo arm) and 3 were randomized comparative studies (no placebo arm). The remaining citation was a nonrandomized comparative study. Three additional prospective studies of interest were identified, of which 2 were randomized controlled studies and 1 was a randomized comparative study. A total of 9 of the 15 studies were controlled and double-masked (Table 1). Six of the 15 studies were rated as level I evidence and the remaining 9 studies were rated as level II evidence.

Randomized Placebo-Controlled Double-Masked Prospective Studies in Aphakic Eyes

Miyake et al[12] (level II) reported on the effects of topical indomethacin 1.0% on incidence of CME in eyes undergoing intracapsular cataract surgery. A total of 112 eyes were randomized to indomethacin and 106 eyes to vehicle placebo. Indomethacin drops were instilled once on the day before surgery, twice on the day of surgery before surgery, and 3 times daily for 2 weeks after surgery. Corticosteroids were administered before and after surgery, but no further details were provided. Fluorescein angiography (FA) was performed at 3 different periods: early (1−2 months after surgery), middle (4−7 months after surgery), and late (12−18 months after surgery). Statistical differences in the cumulative incidence of CME were seen in the early period (51.0% control vs. 25.0% indomethacin) and middle period (21.0% control vs. 11.0% indomethacin), but not in the late period (11.0% control vs. 9.0% indomethacin). Indomethacin-treated eyes had statistically significantly better vision than control eyes in the early period, but not in the middle or late periods.

Yannuzzi et al[13] (level II) conducted a prospective double-masked study of 231 patients undergoing intracapsular cataract extraction randomized either to indomethacin 1.0% (100 eyes) or to vehicle placebo (131 eyes). Medications were administered 4 times daily, beginning with the first day before surgery and extending for 4 to 6 weeks after surgery. Routine corticosteroids were administered per the custom of the operating surgeon, but no further details were provided. Only 59.0% of eyes underwent FA at 5 weeks. Incidence of angiographic CME was statistically significantly less in the indomethacin-treated group compared with the control group at 5 weeks (18.0% vs. 36.0%), but there were no statistically significant differences in the 2 groups by 10 weeks.

Flach et al[14] (level II) reported on the effects of ketorolac 0.50% in preventing angiographic CME in aphakic eyes without concurrent use of corticosteroids. In a paired-comparison study of both eyes of 50 patients undergoing cataract surgery, patients were assigned randomly to 1 of 2 treatment-order groups: ketorolac (first eye) then placebo (second eye), or placebo (first eye) then ketorolac (second eye). One drop (either ketorolac or placebo) 3 times daily was begun 1 day before surgery and continued for 19 days after surgery for a total of 21 days. Nine patients had evidence of unilateral angiographic CME on day 40 after surgery. There was a significant difference favoring ketorolac; only 1 eye treated with ketorolac and 8 eyes treated with placebo demonstrated CME ($P < 0.05$). However, there was no observed beneficial effect of ketorolac therapy on visual acuity.

The studies by both Miyake et al[12] and Yannuzzi et al[13] provide insufficient information on corticosteroid use, which confounds interpretation of the therapeutic effects of indomethacin. Although the study by Flach et al[14] provides more direct evidence (without concurrent corticosteroids) of a short-term therapeutic effect of ketorolac on reducing the incidence of CME in aphakic eyes, application to current practice is difficult because corticosteroids are used commonly. Moreover, advances in modern cataract surgery with the insertion of a posterior chamber intraocular lens have dramatically reduced rates of CME after surgery. All 3 studies demonstrate that postsurgical CME has a tendency to resolve spontaneously and that prophylactic use of topical NSAIDs did not improve visual outcomes beyond 3 months.

Table 1. Effects of Nonsteroidal Anti-inflammatory Drugs on Postoperative Cystoid Macular Edema and Vision: Randomized Double-Masked Placebo-Controlled Studies

Authors, Year	No. of Eyes	Nonsteroidal Anti-inflammatory Drug(s)	Surgery	Cystoid Macular Edema	Vision	Comments
Miyake et al,[12] 1980	218	Indomethacin 1.0%	Aphakic	Early reduction, but not late	Early improvement, but not late	Corticosteroid use was not rigorously documented
Yannuzzi et al,[13] 1981	231	Indomethacin 1.0%	Aphakic	Reduction at 5 wks, but not 10 wks	No difference reported at 1 yr	Poor follow-up
Flach et al,[14] 1990	100 eyes of 50 patients	Ketorolac 0.5%	Aphakic	Reduction at 40 days	No difference	No corticosteroids (paired comparison study)
Kraff et al,[15] 1982	500	Indomethacin 1.0%	ECCE or PE with IOL	Reduction between 2.5 and 5 mos	No difference	All eyes received sub-Tenon and 4 wks of topical corticosteroid
Solomon,[16] 1995	681	Flurbiprofen 0.03% or indomethacin 1.0%	ECCE with IOL	Early reduction of CME, but not late	Early improvement in vision, but not late	Follow-up was not precise and concomitant corticosteroid use was not rigorously documented
Almeida et al,[17] 2012	162	Ketorolac 0.5% or nepafenac 0.1%	PE with IOL	Increased 17.1-μm thickness in placebo eyes	No differences	All eyes received 4 wks of corticosteroid taper
Italian Diclofenac Study Group,[18] 1997	281	Diclofenac 0.1%	ECCE with IOL	Reduction after 36 and 140 days	Not reported	Control eyes had only 5 days of corticosteroid treatment
Singh et al,[30] 2012	263 diabetic patients	Nepafenac 0.1%	PE with IOL	Reduction	Early improvement, but no difference by 90 days	Treatment with nepafenac was for >90 days
Donnenfeld et al,[29] 2006	100	Ketorolac 0.4% (3 different preoperative dosing regimens)	PE with IOL	No significant difference at 2 wks	Eyes pretreated for 1 or 3 days had improved vision	Main point of study was to assess the benefits of pretreatment

ECCE = extracapsular cataract extraction; IOL = intraocular lens; PE = phacoemulsification.

Randomized Placebo-Controlled Double-Masked Prospective Studies in Pseudophakic Eyes

Kraff et al[15] (level I) performed a prospective double-masked trial of 500 patients to assess the effect of topical indomethacin 1.0% on angiographic CME in patients undergoing either nuclear expression or phacoemulsification with implantation of a posterior chamber intraocular lens (PCIOL). Patients were randomized 2:1 to receive either topical indomethacin 1.0% or vehicle placebo the day before surgery (10 doses) and then 4 times daily after surgery for 9 months. All patients received a 40-mg sub-Tenon's injection of methylprednisolone at the end of surgery and self-administered dexamethasone 0.10% 4 times daily for 4 weeks after surgery. Cystoid macular edema was determined by FA: most FA was performed between 2.5 and 5 months. Angiographically confirmed CME was statistically significantly higher in the placebo-treated patients as compared with patients treated with indomethacin (18.50% vs. 9.60%; $P = 0.04$). However, there were no significant differences in the visual acuity after surgery between groups ($P = 0.65$).

Solomon[16] (level I) reported on the efficacy of topical flurbiprofen 0.03% or indomethacin 1.0% in preventing CME. The study population consisted of 681 patients who underwent extracapsular cataract extraction by nuclear expression with PCIOL implantation and were randomized to treatment with flurbiprofen, indomethacin, or vehicle. The assigned drug was instilled into the eye 4 times daily for 2 days before surgery and continued 4 times daily for 3 months after surgery. Concomitant use of prednisolone acetate 1.0% or dexamethasone 0.10% occurred in most eyes after surgery, but no further information was provided. Angiographic and clinical CME (defined as angiographic edema associated with visual acuity $\leq$20/40) were determined at 2 time points after surgery (21–60 days and 121–240 days). There was a statistically significant reduction of angiographic CME at the first time point in the flurbiprofen-treated (16.80%) and indomethacin-treated (12.40%) groups compared with the vehicle group (32.20%). There was also a statistically significant reduction of clinical CME in the flurbiprofen-treated (10.70%) and indomethacin-treated (9.60%) groups compared with the vehicle group (21.90%). However, no statistically significant differences in angiographic or clinical CME were observed by the second time point among treatment groups.

Almeida et al[17] (level I) reported the effects of ketorolac 0.50%, nepafenac 0.10%, or placebo on CME after modern small-incision phacoemulsification with PCIOL placement. A total of 162 patients were assigned randomly in double-masked fashion to ketorolac, nepafenac, or placebo (54 patients per group). Patients were instructed to instill 1 drop of their study drug 4 times daily beginning 1 day before surgery and to continue for 4 weeks after surgery. All patients received prednisolone acetate 1.0% drops 4 times daily for 1 week after surgery, which then was tapered by 1 drop per week. Optical coherence tomography was performed at baseline and at 4 weeks after surgery. No significant increases in retinal thickness from baseline were observed in ketorolac- or nepafenac-treated eyes. There was a modest 17.1-μm increase in placebo eyes ($P < 0.0001$), but there were no significant differences in final visual acuity at 4 weeks among groups.

A multicenter study[18] (level I) involving 8 university or hospital centers and 1 company sponsor (CIBA Vision Ophthalmics; Marcon, Italy) in Italy randomized 141 patients to treatment with diclofenac 0.10% and 140 to placebo after extracapsular cataract

extraction by nuclear expression with PCIOL implantation. All patients received 5 applications of their assigned drug (diclofenac or placebo) before surgery, with installation beginning 3 hours before surgery. Betamethasone was injected subconjunctivally at the end of surgery. Diclofenac-assigned eyes applied 1 drop of their study drug 5 times daily for 5 days after surgery and then 3 times daily until day 140. Control eyes applied 1 drop of dexamethasone 5 times daily for 5 days after surgery and then resumed their study drug 3 times daily until day 140. Fluorescein angiography was performed before surgery and after 36 and 140 days. After 36 days, angiographic CME was found in 9 (6.4%) patients in the diclofenac group and 20 (15.10%) in the control group ($P = 0.03$). After 140 days, CME was present in 4 patients in the diclofenac group (3.30%) and 10 (9.30%) in the control group ($P = 0.05$). No information was provided on visual outcomes.

Although the studies by Kraff et al[15] and Solomon[16] were controlled, timing of follow-up testing was not uniform, which introduces bias, because detection of both onset and resolution of CME is influenced by the duration of follow-up time. In the study by Kraff et al,[15] concomitant use of a sub-Tenon's corticosteroid injection prevents accurate estimation of the isolated therapeutic effect of indomethacin. Solomon's[16] results are limited by variable dosing of topical corticosteroids. The study by Almeida et al[17] reported a small 17-μm increase in retinal thickness on OCT in placebo eyes that was not visually important at 4 weeks; it is noteworthy because modern-day surgical techniques were used with a standard prednisolone acetate 1% dosing regimen and taper after surgery. The multicenter study in Italy[18] reported a lower incidence of angiographic CME after 140 days in diclofenac-treated eyes, but control eyes were markedly undertreated, with only 5 days of corticosteroid therapy. In addition, the study's sponsorship by the manufacturer of diclofenac raises conflict-of-interest concerns. Finally, the study by Kraff et al[15] showed a weak association between angiographic evidence of CME and visual acuity, which has been reported by other investigators[19,20] and emphasizes the inherent limitations of studies that assess angiographic CME as a primary outcome.

Randomized Controlled Prospective Studies

Yavas et al[21] (level II) reported on the effectiveness of topical indomethacin 1.0% to prevent CME. A total of 189 patients were enrolled and underwent uneventful phacoemulsification with insertion of a PCIOL. All patients used topical prednisolone acetate 1% 4 times daily for 1 month after surgery. Eyes were randomized to 1 of 3 groups: indomethacin 4 times daily for 3 days before surgery and 1 month after surgery, indomethacin 4 times daily for 1 month after surgery, and control (no indomethacin). Visual acuity and FA were performed at 3 months. Patients were unmasked, but CME was graded by a masked observer. Angiographic CME was not detected in eyes that received indomethacin before and after surgery. Incidence of angiographic CME was 15.0% in eyes receiving only indomethacin after surgery and 32.80% in the control group ($P < 0.001$). Visual acuity at 3 months in logarithm of the minimum angle of resolution (logMAR) units was significantly better in the group receiving indomethacin before and after surgery (0.02±0.04 logMAR [$20/20^{-1}$ Snellen equivalent]) when compared with indomethacin only after surgery (0.09±0.16 logMAR [$20/25^{+1}$ Snellen equivalent]; $P = 0.005$) or control (0.11±0.12 logMAR [$20/25^{-1}$ Snellen equivalent]; $P < 0.001$).

Both control eyes and indomethacin-treated eyes had much higher rates of angiographic CME than typically reported in the literature at 3 months after modern uncomplicated cataract surgery. This may reflect the more subjective qualitative nature of CME grading on FA. Confirmation of angiographic CME rates was not possible because of the lack of concurrent objective quantitative OCT macular thickness measurements. Although the study demonstrated a visual benefit at 3 months in eyes receiving indomethacin before and after surgery, the absolute difference in visual acuity was small. Furthermore, visual acuity was measured using Snellen visual acuity charts, and no details were provided on whether refraction was performed consistently.

Randomized Comparative Prospective Studies

Miyake et al[22] (level II) compared nepafenac 0.10% versus fluorometholone 0.10% in preventing CME after modern small-incision phacoemulsification with PCIOL insertion. A total of 30 patients were randomized to nepafenac and 29 patients to fluorometholone in a double-masked fashion. Patients received 1 drop of their study drug 3 times daily starting 1 day before surgery until 5 weeks after surgery. An additional drop was given on the day of surgery. No other anti-inflammatory medications were administered. Both FA and OCT were performed at 5 weeks. The incidence of CME determined on FA at 5 weeks was 14.30% in the nepafenac group and 81.50% in the fluorometholone group ($P < 0.0001$). Mean foveal thickness also was significantly less at 5 weeks in the nepafenac group (194.3 μm) compared with the fluorometholone group (220.1 μm; $P = 0.006$). A significantly greater number of nepafenac-treated eyes showed improvement of visual acuity at 5 weeks from baseline compared with fluorometholone-treated eyes ($P = 0.04$).

Wittpenn et al[23] (level I) reported on a randomized investigator-masked comparison of topical ketorolac 0.40% plus corticosteroid compared with corticosteroid alone in patients undergoing small-incision phacoemulsification with PCIOL insertion. A total of 278 patients who were considered to be at low risk for CME were randomized to prednisolone acetate 1.0% 4 times daily for 4 weeks after surgery; another 268 patients were randomized to ketorolac 0.40% 4 times daily for 3 days before surgery and then prednisolone acetate 1.0% plus ketorolac 0.40%, each 4 times daily for 4 weeks after surgery. A significantly reduced rate of OCT-based CME with combination treatment was observed ($P = 0.018$) at 4 weeks. However, the absolute incidence of definite or probable CME was low in both groups (2.40% for the corticosteroid group; 0.0% for the ketorolac plus corticosteroid group), and there was no difference reported in Snellen visual acuity outcomes at 4 weeks.

Wang et al[24] (level II) reported on a prospective trial that randomized eyes to treatment with bromfenac 0.10%, fluorometholone 0.10%, or dexamethasone 0.10%. A total of 240 patients undergoing small-incision phacoemulsification with PCIOL insertion were randomized to 1 of 4 postsurgical treatment groups: bromfenac 0.10% twice daily for 1 month, bromfenac 0.10% twice daily for 2 months, fluorometholone 0.10% thrice daily for 1 month, or

dexamethasone 0.10% thrice daily for 1 month. The study was unmasked, and no topical anti-inflammatory drugs were applied before surgery. All patients received 15 mg prednisone daily for 7 days after surgery. At 2 months, mean foveal retinal thickness determined by OCT was significantly less in both bromfenac groups. Mean thickness was 208.51 μm and 210.45 μm in the 1-month and 2-month bromfenac groups, respectively, compared with 239.49 μm and 241.29 μm in the fluorometholone and dexamethasone groups, respectively. Despite these differences in retinal thickness, there were no significant differences in visual acuity reported among groups.

Asano et al[25] (level II) reported on a randomized double-masked study comparing the effects of diclofenac sodium 0.10% versus betamethasone 0.10% in preventing CME after modern small-incision phacoemulsification with PCIOL insertion. A total of 142 patients were randomized to receive either diclofenac (71 patients) or betamethasone (71 patients) for 8 weeks. A total of 4 applications of study drug were applied, beginning 3 hours before surgery and then continued 3 times daily for 8 weeks. No other anti-inflammatory drugs were administered. Angiographic CME was detected in 18.8% of eyes in the diclofenac group and in 58.0% of eyes in the betamethasone group ($P < 0.001$) at 5 weeks. However, there were no significant differences in vision between groups out to 8 weeks.

Both studies by Miyake et al[22] and Wang et al[24] demonstrate a short-term therapeutic effect of nepafenac and bromfenac when compared with fluorometholone in reducing the incidence of angiographic CME and OCT-based retinal thickening, but fluorometholone formulations used in both studies (without acetate) have very limited intraocular penetration. Therefore, these results may approximate more closely the effectiveness of these NSAIDs as compared with placebo.[8,26] In addition, only a modest visual benefit was reported with nepafenac treatment at 5 weeks. The study by Wittpenn et al[23] reported a low incidence of OCT-based CME in the group treated with corticosteroids alone and no difference in visual acuity with or without concomitant NSAID treatment. This latter study's results question the cost effectiveness of adding prophylactic NSAID treatment to corticosteroids in patients at low risk of CME.[27] Asano et al[25] reported no differences in vision, but a large difference in angiographic-determined CME, between the diclofenac (18.8%) and betamethasone (58.0%) treatment groups, consistent with a weak association between angiographic evidence of CME and visual acuity.[15,19,20] None of the above studies demonstrated a visual benefit of NSAID treatment beyond 5 weeks.

Other Prospective Studies of Interest

A multicenter, prospective study by Miyake et al[28] (level II) compared the effects of topical diclofenac 0.10% versus fluorometholone 0.10% for the prevention of CME in eyes undergoing modern small-incision phacoemulsification with PCIOL insertion. Treatment assignment was not randomized and patients were not masked. Fifty-three eyes received diclofenac and 53 eyes received fluorometholone. A total of 4 drops were applied on the day of surgery beginning 3 hours before and then 3 times daily for 8 weeks after surgery. No other anti-inflammatory medications were administered. Cystoid macular edema based on FA results was graded by a masked investigator. Five weeks after surgery, angiographic CME was present in 5.70% of diclofenac-treated eyes and in 54.70% of fluorometholone-treated eyes ($P < 0.001$), but there were no statistically significant differences in visual acuity.

Donnenfeld et al[29] (level II) reported on the effects of different preoperative dosing regimens of ketorolac 0.40% on postoperative CME and visual acuity. A total of 100 patients undergoing phacoemulsification with PCIOL insertion were randomized in double-masked fashion to 1 of 4 groups to receive ketorolac for 3 days (group 1), 1 day (group 2), or 1 hour (group 3) before cataract surgery or a placebo (group 4) before cataract surgery. Groups 1, 2, and 3 received ketorolac 4 times daily for 3 weeks after surgery. Group 4 received the vehicle placebo for 3 weeks after surgery. All eyes received topical prednisolone acetate 1.0% 4 times daily for 2 weeks and then twice daily for 1 week after surgery. Optical coherence tomography testing was performed at 2 weeks only if visual acuity was worse than 20/30. Cystoid macular edema was determined by OCT with no further information about methodology or definition provided. At 2 weeks, no eyes using ketorolac for 1 or 3 days before surgery had CME compared with 12.0% of control eyes and 4.0% of patients in the 1-hour group, but differences were not statistically significant. Eyes pretreated with ketorolac for 1 day (approximately 0.05 logMAR [$20/20^{-2}$ Snellen equivalent]) or 3 days (approximately 0.03 logMAR [$20/20^{-1}$ Snellen equivalent]) had significantly better visual outcomes at 2 weeks compared with control eyes (approximately 0.13 logMAR [$20/25^{-2}$ Snellen equivalent]; $P = 0.007$), but this difference did not persist by 3 months. These results suggest that use of an anti-inflammatory medication for up to 3 days before surgery hastens visual recovery in the immediate period after cataract surgery, but it does not affect visual outcomes at 3 months after surgery.

Prospective Studies in Diabetic Patients

Singh et al[30] (level I) reported on the results of a multicenter randomized double-masked placebo-controlled study of 263 diabetic patients with nonproliferative diabetic retinopathy undergoing cataract surgery. Patients were randomized 1:1 to instill nepafenac 0.10% or vehicle 3 times daily beginning 1 day before surgery through day 90. All patients used prednisolone acetate 1.0% 4 times daily for 2 weeks after surgery. Macular edema was defined as an increase of 30% or more in OCT central subfield thickness from presurgical baseline. A significantly greater percentage of patients in the vehicle group compared with the nepafenac group developed macular edema at day 30 (8.70% vs. 2.40%; $P = 0.029$), day 60 (15.10% vs. 2.40%; $P < 0.001$), and day 90 (16.70% vs. 3.20%; $P < 0.001$). Visual acuity results, reported as percent decrease of more than 5 letters, also significantly favored nepafenac-treated eyes compared with vehicle at day 30 (2.4% vs. 14.8%; $P < 0.001$) and day 60 (2.4% vs. 13.1%; $P = 0.002$), but differences were no longer significant by day 90 (5.6% vs. 11.5%; $P = 0.102$).

Singh et al[30] rigorously assessed vision by certified technicians using Early Treatment Diabetic Retinopathy Study acuity charts in a higher-risk group of diabetic patients and relied on OCT-based assessment using percent change in central subfield thickness from the presurgical baseline, which may be a more objective means of assessing retinal thickening after cataract surgery.[3,31] This study showed that nepafenac reduced the incidence of macular edema at all time points and resulted in better visual acuity (defined as percent decrease of more than 5 letters) at 30 and 60 days after surgery. However, control eyes were treated after surgery only for 2 weeks with prednisolone acetate 1%, whereas nepafenac-treated eyes received more than 90 days of therapy (including before surgery) in addition to 2 weeks of prednisolone acetate 1%. Despite this large discrepancy in treatment, a visual benefit in nepafenac-treated eyes was not observed at 90 days, which was the primary outcome of this study.

Conclusions

Although NSAIDs clearly are effective in reducing the incidence of angiographic or OCT-based CME and hastening visual recovery in the short term (<3 months) when compared with placebo or topical corticosteroid formulations that have poor corneal penetration (e.g., fluorometholone 0.10%), there is no level I evidence to suggest that prophylactic use of NSAIDs reduces longer term (e.g., >3 months) vision loss from CME after cataract surgery. The body of level II evidence supports the same conclusion. The claim made by several authors that use of an NSAID and corticosteroid is synergistic, with the implication that the combined effect of each drug class exceeds the additive effect of each drug, is not supported by the literature. This clinical impression of synergy remains unproven and seems unlikely given the overlapping mechanisms of the drugs.[27]

The primary objective of this assessment was to evaluate the effect of NSAID administration on visual acuity at 3 months or more after routine cataract surgery. Methodologic limitations of the studies reviewed prevent any conclusions of a clear benefit for NSAID (alone or in conjunction with corticosteroid) therapy in reducing vision loss from CME. Many studies, for example, focused on reduction of angiographic CME as a primary outcome, which is largely historic because of the rapid emergence of OCT and which is problematic because angiographic CME does not correlate strongly with visual acuity.[15,19,20,25] In addition, more sensitive visual acuity functional tests, such as contrast sensitivity, are lacking. Furthermore, several studies may have favored NSAID treatment by preferentially pretreating a group of eyes with an NSAID, but in turn, not pretreating comparison eyes with an alternative anti-inflammatory medication.[15–18,23,30] In other studies, some eyes were treated with both an NSAID and a corticosteroid and then compared with eyes treated with a corticosteroid alone without any adjustment made for dosing disparities. For example, in the study by Wittpenn et al,[23] patients in the ketorolac plus steroid group received dosing of both medications 4 times daily (8 total applications) compared with only 4 applications of the corticosteroid in the steroid only group.

Many retina specialists and cataract surgeons believe that CME after cataract surgery usually resolves spontaneously and that mild leakage on FA or minimal cystoid changes and retinal thickening on OCT may be compatible with good vision.[8] Therefore, studies assessing a therapeutic effect of NSAIDs should be controlled, should focus on primarily longer-term visual outcomes (≥3 months), and should perform rigorous assessments of best-corrected visual acuity with refraction by certified technicians using standardized Early Treatment Diabetic Retinopathy Study acuity charts. Including contrast sensitivity testing may add further visually relevant data to the effects of managing transient CME after cataract surgery. None of the studies in this review satisfied these criteria.

Even more difficult to support is the claim made by several authors that use of an NSAID and corticosteroid is synergistic.[32,33] Synergy in medicine is best defined as the interaction of 2 or more drugs to produce an effect greater than the sum of their individual effects. A classic example of synergy involves the use of penicillin and aminoglycoside antibiotics: use of both drug classes via different mechanisms of action in combination significantly lowers the median inhibitory concentration of each antibiotic for a given micro-organism.[27] Although previous studies have suggested that NSAIDs may facilitate a greater re-establishment of the blood-aqueous barrier than corticosteroids, key differences in drug concentration and pharmacokinetics preclude any conclusions about synergy.[34] Although studies consistently demonstrate a greater therapeutic effect in reducing CME and improving vision in the short term with the combined use of an NSAID and corticosteroid compared with corticosteroid treatment alone, this can be explained by an additive effect of 2 anti-inflammatory drugs, which therefore may be replicated by increased dosing of a single agent. Although several studies have reported that in addition to their anti-inflammatory effects, NSAIDs also reduce surgical miosis and pain after cataract surgery, corticosteroids seem to possess similar therapeutic benefits.[35,36]

Corticosteroids have broader anti-inflammatory effects than NSAIDs and a much longer track record of use, which has led most surgeons to be reluctant to substitute NSAIDs for corticosteroids to control inflammation after cataract surgery. Nevertheless, corticosteroid formulations vary substantially in their anti-inflammatory effects within the eye because of differences in concentration, innate glucocorticoid activity (Table 2), and lipophilicity.[26,37,38] Fluorometholone alcohol 0.10% has limited intraocular penetration. Betamethasone sodium phosphate 0.10% and dexamethasone alcohol 0.10% have significantly less mean peak aqueous concentration (7.70 ng/ml and 31.0 ng/ml, respectively) after a single topical application than prednisolone acetate 1.0% (669.6 ng/ml), and therefore may have less profound intraocular anti-inflammatory effects despite possessing greater intrinsic glucocorticoid activity (Table 3).[26] Recognizing these differences among corticosteroid formulations is necessary to interpret the

Table 2. Relative Glucocorticoid Activity of Corticosteroids

Corticosteroid	Equivalent Potency (mg)*	Anti-inflammatory Potency†
Hydrocortisone	20.00	1
Prednisolone	5.00	4
Fluorometholone	Not available	25–30
Dexamethasone	0.75	30
Betamethasone	0.60–0.75	25

*A measure of how much the hypothalamic-pituitary-adrenal axis is suppressed.
†Glucocorticoid activity relative to hydrocortisone.

SOURCES: Morrison E, Archer DB. Effect of fluorometholone (FML) on the intraocular pressure of corticosteroid responders. Br J Ophthalmol 1984;68:581–4; and Flynn M, Hebel SK. Drug Facts and Comparison. 51st ed. St. Louis, MO: Lippincott Williams and Wilkins; 1997;122–3.

Table 3. Mean Peak Aqueous Concentration after Single Application

Corticosteroid Formulation	Aqueous Humor Concentration (ng/ml)
Prednisolone acetate 1%	669.9
Fluorometholone alcohol 0.1%	5.1
Dexamethasone alcohol 0.1%	31.0
Betamethasone sodium phosphate 0.1%	7.7

SOURCE: McGhee CN, Watson DG, Midgley JM, et al. Penetration of synthetic corticosteroids into human aqueous humour. Eye (Lond) 1990;4(Pt 3):526–30.

therapeutic effect of comparative or combination NSAID treatment properly.

Donnenfeld et al[29] investigated timing of NSAID treatment and demonstrated that use for up to 3 days before cataract surgery hastens visual recovery in the immediate period after surgery. These results are consistent with other published reports that demonstrate a short-term therapeutic benefit in regard to vision and reduction of CME with use of an NSAID before surgery.[6,8] Although prostaglandins have short half-lives, clinically important inhibition of cyclooxygenase enzyme probably requires sustained inhibitory drug levels that are not obtained immediately after initial application. Therefore, continual use of either an NSAID or corticosteroid for several days before surgery should achieve sustained intraocular levels sufficient to inhibit meaningful prostaglandin synthesis at the time of surgery. Consequently, there is good collective clinical evidence and rationale that application of an anti-inflammatory drug for 3 days before surgery reduces CME and improves vision in the short term, but there is no evidence that this practice affects long-term outcomes.

To date in the literature, there is no universally accepted method for reporting CME. Several studies relied on angiographic determination of CME, which is problematic because qualitative subjective angiographic grading of CME relates poorly with visual acuity.[3,15,25] In contrast, OCT determination of CME is more objective, quantitative, and noninvasive.[3] More importantly, several researchers have reported that increased retinal thickness is associated more strongly with visual acuity than the presence of leakage on FA.[3,19,20] Despite these potential advantages, there is no universally accepted method of reporting CME based on OCT, which results in wide ranges of incidence and

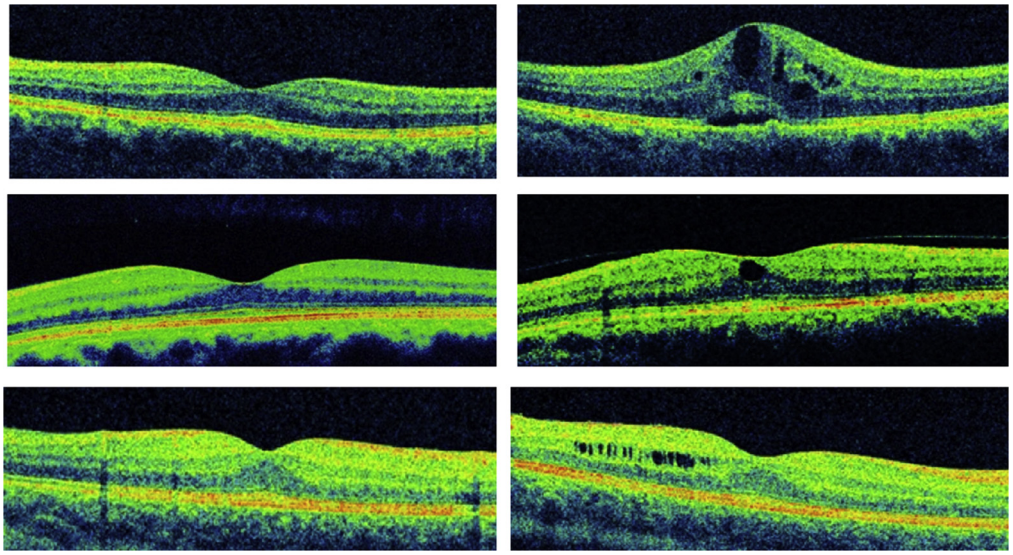

Figure 1. Optical coherence tomography images of 3 representative cataract surgery patients: (left column) before surgery and (right) after surgery. **Top row**, large cystoid changes and subretinal fluid with increase in central subfield (CSF) thickness of 119% (599 μm) from baseline (274 μm) and $20/60^{+1}$ visual acuity. **Middle row**, foveal cyst with 23% (312 μm) increase in CSF thickness from baseline (254 μm) and $20/25^{+2}$ visual acuity. **Bottom row**, intraretinal cystoid changes outside of the fovea with 2% (345 μm) increase in CSF thickness from baseline (339 μm) and $20/20^{-1}$ visual acuity. Note that presurgical baseline CSF thickness varied by 85 μm among patients. Using a 30% or more change in CSF thickness from baseline, as used by Singh et al,[30] identified only the eye in the top row as developing clinically important cystoid macular edema. (Courtesy of Stephen J. Kim, MD.)

confounds assessment of treatment effect. Wittpenn et al[23] stratified CME into definite, probable, and possible types based entirely on grader interpretation of cystoid changes and retinal contour on OCT. In contrast, Wang et al[24] defined CME as central thickness of more than 250 μm with intraretinal cystoid changes underneath the fovea. Singh et al[30] used percent change in OCT central subfield thickness from the presurgical baseline. This has been proposed as a more objective method of reporting clinically important CME that minimizes interpatient and interinstitution variability, and it automatically adjusts for the normal variation (as much as 100 μm) in retinal thickness that exists among healthy eyes.[31,39] Moreover, this latter definition does not rely on cystoid changes, which require interpretation and which may not be clinically important if mild or present outside the fovea (Fig 1).

As with all literature reviews, the findings of this assessment should be interpreted with caution and may not be generalizable to patients possessing characteristics different from patients enrolled in the studies reviewed. For example, patients with higher-risk characteristics such as uveitis or diabetic macular edema generally were excluded. Although long-term visual acuity (≥3 months) after cataract surgery is an important clinical measure of a therapeutic intervention, this assessment was not designed to comment on the rationale and potential value of NSAID therapy in preventing CME soon after surgery and the patient satisfaction and quality-of-life improvement associated with more rapid visual rehabilitation.

In conclusion, there is a lack of level I evidence that supports the long-term visual benefit of NSAID therapy when applied solely or in combination with corticosteroid therapy to prevent vision loss resulting from CME after cataract surgery. The implication that the combined effect of NSAIDs and corticosteroids exceeds the additive effect of each drug is not supported by the literature. Dosing of NSAIDs before surgery seems to hasten visual recovery after cataract surgery, but does not affect long-term visual outcomes. Lack of a validated and universally used definition of CME limits accurate estimation of its incidence and assessment of treatment benefit with cross-trial comparisons.

Future Research

Because CME resolves spontaneously and can be compatible with good vision in mild cases, future trials should be controlled and primarily should focus on long-term visual outcomes, quality-of-life measures in the early postoperative period, and cost of care. Best-corrected visual acuity should be assessed rigorously by means of refraction by trained technicians using standardized Early Treatment Diabetic Retinopathy Study acuity charts, and the addition of contrast sensitivity testing should be considered. Optical coherence tomography determination of CME should be emphasized, and obtaining baseline retinal thickness before surgery and reporting CME in percent change in thickness from baseline should be encouraged to allow more uniform accounting of disease incidence. Investigational trials should account fully for dosing disparities between comparative groups to allow balanced assessment of treatment benefit. Potential conflicts of interest should be avoided. Finally, a single corticosteroid formulation and regimen should be advocated in future studies to allow for more straightforward comparison of results among different studies.

Note Added in Proof. While this paper was under review, Tzelikis et al[40] reported that prophylactic use of nonsteroidal anti-inflammatory drugs, ketorolac (0.4%) and nepafenac (0.1%), were not efficacious in preventing macular edema compared with placebo after uneventful cataract surgery when evaluated by OCT in a prospective randomized study, which corroborates the findings of this evidence-based review.

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Abbreviations and Acronyms:
CME = cystoid macular edema; **FA** = fluorescein angiography; **FDA** = Food and Drug Administration; **logMAR** = logarithm of the Minimum Angle of Resolution; **NSAID** = nonsteroidal anti-inflammatory drug; **OCT** = optical coherence tomography; **PCIOL** = posterior chamber intraocular lens.

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