Incidence of visually significant pseudophakic macular edema after uneventful phacoemulsification in patients treated with nepafenac

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PURPOSE: To compare the incidence of visually significant pseudophakic macular edema after uneventful phacoemulsification in patients treated postoperatively with topical prednisolone and those treated with topical prednisolone and nepafenac 0.1% suspension (Nevanac).

SETTING: Edward S. Harkness Eye Institute of Columbia University, New York, New York, USA.

METHODS: This retrospective chart review was of consecutive patients who had phacoemulsification at a single institute and were given topical prednisolone alone or topical prednisolone and nepafenac to prevent cystoid macular edema. Data collection included preexisting ocular and systemic diseases, concurrent use of ocular and systemic medications, surgical technique, intraoperative and postoperative complications, follow-up visual and ocular assessments, and postoperative optical coherence tomography (OCT) assessment for macular edema.

RESULTS: Postoperatively, 240 patients were treated with prednisolone and 210 patients, with prednisolone–nepafenac. Preoperatively, the 2 groups were demographically and clinically comparable in sex distribution ($P = .8400$), history of diabetes ($P = .7267$), hypertension or cardiac disease ($P = .8690$), and concurrent use of oral nonsteroidal anti-inflammatory drugs ($P = .7303$). Iris manipulation was done in 16 patients in the prednisolone-alone group and 10 patients in the prednisolone–nepafenac group ($P = .3876$). Capsule staining was done in 5 patients and 4 patients, respectively. All patients were followed for at least 1 month postoperatively. Visually significant pseudophakic macular edema was documented by OCT in 5 patients treated with prednisolone alone and in no patients treated with prednisolone and nepafenac ($P = .0354$). No significant intraoperative or postoperative complications were reported.

CONCLUSION: Patients treated with topical prednisolone alone had a significantly higher incidence of visually significant pseudophakic macular edema after uneventful cataract surgery than those treated with topical prednisolone and nepafenac.

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Modern cataract extraction and posterior intraocular lens (IOL) implantation procedures are extremely safe and successful; however, complications arising from prostaglandin-mediated inflammation still occur. Cystoid macular edema (CME) resulting from inflammation and subsequent breakdown of the blood–aqueous barrier (BAB) is the most common cause of decreased vision postoperatively in uneventful cataract surgery.[1,2] The peak incidence of CME after surgery varies between 4 weeks and 12 weeks.[3,4] Macular edema is often asymptomatic, as evidenced by a greater incidence of angiographic CME than of visually significant CME.[5] Associated losses in vision are usually self-limited and resolve spontaneously; however, how long a patient's vision is affected can significantly limit and affect daily activities and a lag time in recovery of visual function can be observed even after the inflammation has resolved.[3]

Steroid compounds to prevent and treat CME after cataract surgery have been studied. However, the efficacy of these agents in preventing CME in all cases has not been demonstrated.[1] In addition, topical ocular steroids are associated with certain risks, such as glaucoma, cataracts, opportunistic infections, and delayed wound healing.[6,7] Subsequently, nonsteroidal anti-inflammatory drugs (NSAIDs) have been studied as

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adjunctive and alternative agents for preventing macular edema. There are 7 major categories of NSAIDs, with indole (indomethacin), phenylacetates (diclofenac), and phenylalkanoic acid (flurbiprofen, suprofen, ketorolac) being the classes most commonly used in ophthalmology (Table 1).[7] Topical ocular NSAIDs are postulated to decrease the development of CME after cataract surgery based on their ability to reduce prostaglandin production and the subsequent effects on the BAB. Although the U.S. Food and Drug Administration has not approved any NSAID for the prevention or treatment of CME, several studies have evaluated the efficacy of these agents for this indication.[3,8–17]

The purpose of this study was to evaluate the efficacy of nepafenac, a prodrug arylacetic acid NSAID introduced in 2005, in preventing visually significant pseudophakic macular edema after cataract surgery and review the results in relation to the current literature on NSAIDs for the prevention of CME after uneventful cataract surgery.

Table 1. Nonsteroidal anti-inflammatory agents by classification (modified from Samiy and Foster[6]).

Class of NSAID	Generic Name
Salicylates	Aspirin
	Diflunisal
Fenamates	Mefanamate
	Meclofenamate
Indoles	Indomethacin
	Sulindac
	Tolmentin
Phenylacetic acid	Diclofenac
Phenylalkanoic acids	Fenoprofen
	Ketoprofen
	Piroxicam
	Flurbiprofen
	Ketorolac
	Naproxen
	Ibuprofen
Pyrazolones	Phenylbutazone
	Oxyphenybutazone
Paraminophenols	Acetaminophen

NSAID = nonsteroidal anti-inflammatory drug

PATIENTS AND METHODS

This retrospective chart review was of consecutive patients who had phacoemulsification and were treated postoperatively with topical prednisolone alone or topical prednisolone with nepafenac at the Edward S. Harkness Eye Institute of Columbia University College of Physicians and Surgeons, New York, New York, from 2004 to 2006. The study was approved by the Columbia University Institutional Review Board and was conducted in compliance with all patient privacy regulations. The primary endpoint of the study was evaluation of visually significant CME, defined by cystic changes evident on ocular coherence tomography (OCT) in patients with compromised visual acuity 1 month after uneventful cataract extraction with IOL implantation.

Study patients received prednisolone alone or nepafenac and prednisolone after uneventful phacoemulsification with IOL implantation. The postoperative regimen for the prednisone-alone group was 1 drop 4 times daily for 1 week, then tapered to 3 times daily for 1 week, twice daily for 1 week, and once daily for 1 week. In the prednisolone–nepafenac group, prednisolone dosing was identical and patients also received 1 drop nepafenac 3 times daily for 4 weeks.

Data collection included preexisting ocular and systemic diseases, concurrent use of ocular and systemic medications, surgical technique, intraoperative and postoperative complications, follow-up visual and ocular assessments, and postoperative OCT assessment for macular edema. All phacoemulsification surgeries were performed by the same physician (R.E.B.) using the Infiniti phaco machine (Alcon).

Snellen visual acuity and intraocular pressure were measured 1, 7, and 30 days postoperatively. A slitlamp examination was also performed at these visits. A dilated fundus examination was conducted 1 month after surgery. Best corrected visual acuity (BCVA) was assessed 1 month after therapy. If refraction revealed suboptimal BCVA not explained by posterior capsule opacification, preexisting corneal disease, or preexisting maculopathy, OCT was performed. Of note, OCT was done regardless of what was revealed on slitlamp biomicroscopy–fundus examination (ie, even if the retina appeared flat, OCT was done to detect subclinical cystic changes that could contribute to suboptimal vision). The OCT was then interpreted by R.E.B. with assistance from a member of the retina faculty if the OCT results were ambiguous. If cystic changes were evident, the patient was started on a regimen of nonsteroidal anti-inflammatory and steroid drops.

RESULTS

Four hundred fifty charts were reviewed, including those of 240 patients who received prednisolone alone and 210 patients who received prednisolone–nepafenac treatment. All patients had at least 1 month of follow-up. Patients ranged in age from 44 to 91 years old. Preoperatively, the 2 groups were demographically

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and clinically comparable in sex distribution, history of diabetes, hypertension or cardiac disease, and concurrent use of oral NSAIDs (Table 2). Iris manipulation was done in 16 patients in the prednisolone-alone group and 10 patients in the prednisolone–nepafenac group ($P = .3876$). Capsule staining was performed in 5 patients and 4 patients, respectively. No significant intraoperative complications were reported in either treatment group.

Visually significant pseudophakic macular edema was documented by OCT in 5 patients treated with prednisolone alone and in no patient treated with prednisolone and nepafenac ($P = .0354$). Of the 5 patients who developed CME in the prednisolone-alone group, 2 were men and 3 women; none had iris manipulation, capsule staining, or a diagnosis of diabetes; and 3 had a diagnosis of hypertension or cardiac disease. One patient was receiving concurrent aspirin therapy.

No significant postoperative complications were reported in either group. One patient initially in the prednisolone–nepafenac group was taken off nepafenac on postoperative day 1 because of a corneal epithelial defect. This patient, excluded from data analysis, later developed OCT-documented visually significant CME.

DISCUSSION

Several studies have shown that topical ocular NSAIDs are effective in preventing angiographic CME in pseudophakic and aphakic patients with and without concurrent steroid therapy.[5] Although many of these trials lacked rigorous design, results in several well-controlled trials with NSAIDs (indomethacin, diclofenac, and ketorolac) for the prevention of angiographic CME show an overall benefit.[3,8–17] Within these studies, NSAIDs were generally dosed concurrently with topical ocular steroids, although at least 1 trial evaluating ketorolac monotherapy also demonstrated a benefit.[14]

Table 2. Summary of baseline patient characteristics.

Characteristic	Number		*P* Value
	Prednisolone Alone	Prednisolone –Nepafenac	
Sex			.8400
Male	112	100	
Female	128	110	
History of diabetes	43	35	.7267
History of cardiac disease	107	92	.8690
Concurrent NSAID use	64	53	.7303

NSAID = nonsteroidal anti-inflammatory drug

Despite the evidence that NSAIDs are effective in preventing angiographic CME, a clear correlation between angiographic CME and clinically meaningful visual loss has not been established.[1] Evaluating the impact of NSAID treatment on clinical CME (visually significant) is important because loss of vision associated with macular edema significantly affects patient outcomes and perceptions after surgery. To date, the only studies that have demonstrated a statistically significant effect on visual acuity associated with CME have evaluated older NSAIDs (eg, indomethacin suspended in sesame seed oil and flurbiprofen) currently not available or uncommon in clinical practice.[9,13] However, the findings in a metaanalysis showing an overall positive effect of topical NSAID treatment on clinically significant CME (defined as clinically diagnosed CME or grade III angiographic edema with associated visual loss) supports a therapeutic benefit with other agents.[2] Another important consideration is that none of these studies found a statistically significant effect on vision beyond 3 months. Failure to detect differences in visual acuity at later time points may be explained by the self-limiting nature and overall lower incidence of CME farther out from surgery, which decreases the power to detect treatment differences.

Nepafenac is a neutral prodrug with superior permeability characteristics compared with other available topical NSAIDs. An in vitro study using rabbit tissue found greater permeability of nepafenac over diclofenac (6-fold greater permeation coefficient) and no lag period for absorption.[18] Greater permeability results in less active drug exposure to the cornea and greater drug concentration at the site of action. Due to its prodrug property, a reservoir of parent drug that is later converted to amfenac may be created in the anterior chamber of the eye, prolonging the duration of the anti-inflammatory action. Whether this property translates into superior efficacy in CME prophylaxis compared with that of other currently marketed NSAIDs is unknown. In addition, since corneal contact time of NSAIDs may be associated with corneal toxicity, decreased concentrations of nepafenac on the corneal surface may provide an added safety advantage over other conventional NSAIDs.[4] Nepafenac has demonstrated efficacy in reducing inflammation in the period after cataract surgery, although its effectiveness in preventing angiographic or clinical CME had not previously been studied (Product Monograph. Nevanac. Alcon Laboratories, Inc., Ft. Worth, Texas, 2006).

The purpose of the present study was to evaluate the effectiveness of nepafenac in preventing visually significant CME after cataract surgery. Our results show a reduction in visually significant CME in patients treated with nepafenac and prednisolone compared with patients treated with prednisolone alone (0% and 2%, respectively; $P = .0354$), supporting the addition of topical ocular nepafenac

therapy to standard postoperative steroid agents. Our study adds to the current evidence supporting the benefit of NSAID therapy combined with topical ocular steroids for the prevention of visually significant CME.[9,13] The use of nepafenac alone after cataract surgery to prevent visually significant CME or the effectiveness of nepafenac in reducing angiographic CME still has to be evaluated in other trials. In addition, our study failed to evaluate the effect of treatment beyond 1 month after surgery. Questions remain regarding the effectiveness of NSAID treatment on visually significant CME beyond 3 months.

Our study was limited by its retrospective nonrandomized design as well as by the limited follow-up period. The results in nonrandomized retrospective studies should be interpreted cautiously. Retrospective studies can introduce bias in patient selection and timing of events. We evaluated several baseline confounding variables that may contribute to the overall occurrence of CME postoperatively and saw no difference between treatment groups. In addition, an objective endpoint of visual acuity loss was assessed in our study to minimize bias. It is possible that other confounding variables not accounted for in our data collection contributed to the results or that there was bias in the OCT readings.

Recent evidence supports that glare and contrast sensitivity testing may be more sensitive measures than Snellen visual acuity of vision loss associated with CME. In a randomized double-masked control study of flurbiprofen and indomethacin treatment in patients having extracapsular cataract extraction with posterior chamber IOL implantation, Snellen visual acuity differences of 2 lines or more were not significantly different between treatment groups, although a statistically significant difference in contrast sensitivity between treatment groups and a placebo group was observed.[3] This improvement in contrast sensitivity measures was evident in patients with or without CME, although the greatest benefit was observed in CME patients. Based on contrast sensitivity results, what the influence of nepafenac treatment would be is unknown.

Overall, after uneventful cataract surgery, patients treated with topical prednisolone alone had a significantly higher incidence of visually significant pseudophakic macular edema than those treated with topical prednisolone and nepafenac. However, the positive effect of nepafenac treatment on preventing visually significant clinical CME should be confirmed in follow-up prospective controlled studies.

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