The Role of NSAIDs in the Management of Macular Edema

by Angela P. Bessette, MD, and Rishi P. Singh, MD

Nonsteroidal anti-inflammatory drugs (NSAIDs) are potent inhibitors of the enzyme, cyclooxygenase (COX), a key catalyst in the inflammatory pathway. As such, they are widely utilized by physicians for their analgesic, antipyretic, and anti-inflammatory properties. Activation of the COX pathway leads to the production of prostaglandins. Within the eye, prostaglandins promote miosis, vasodilation, disruption of the blood-ocular barrier, and leukocyte migration.1 Ophthalmologists commonly use topical NSAIDs to decrease postoperative inflammation, limit intraoperative miosis, and prevent and treat macular edema associated with cataract surgery.1 Several topical preparations of NSAIDs are currently available for ophthalmic use, including flurbiprofen, diclofenac, ketorolac, bromfenac, and nepafenac. Newer NSAIDs, including bromfenac and nepafenac, were formulated to have greater corneal penetration and, in preclinical studies, were shown to have higher concentrations in ocular tissues, including the retina.1,3 Given the potential for better drug delivery to the posterior segment with newer NSAIDs and a growing body of evidence that implicates inflammation in the pathogenesis of macular edema associated with diabetes and retinal vein occlusions (RVOs),1,5 there is renewed interest in the role of topical NSAIDs to treat retinal disease.

PROPHYLAXIS OF PSEUDOPHAKIC MACULAR EDEMA

Cystoid macular edema (CME) is a common cause of vision loss following cataract surgery, especially in patients with uveitis or diabetes. NSAIDs are commonly prescribed by cataract surgeons in the perioperative period, and many studies have evaluated their effect on surgical outcomes. Pretreatment with NSAIDs for 1 day to 3 days...
prior to cataract surgery has been shown to give better visual acuity outcomes in the immediate postoperative period compared to placebo; however, the effects are lost by 90 days. The role of NSAIDs in preventing macular edema related to cataract surgery is controversial. In a multicenter, placebo-controlled trial in patients with nonproliferative diabetic retinopathy (NPDR), nepafenac 0.1% decreased the incidence of postoperative macular edema within 90 days of cataract surgery and showed early visual acuity benefits. These results have since been supported by two multicenter, vehicle-controlled trials of nepafenac 0.3% in patients with NPDR in which the pooled analysis of the efficacy endpoints showed a significant number of nepafenac-treated patients achieving a three-line gain in visual acuity versus vehicle-treated patients. These studies led to the approval of nepafenac by the European Medicines Agency for the prevention of macular edema in patients with diabetes undergoing cataract surgery. Nepafenac has also recently been labeled in the United Kingdom for the prevention of macular edema following cataract surgery in diabetic patients.

The evidence for NSAID use in routine cataract surgery in nondiabetic patients is less compelling. A prospective, randomized, controlled trial comparing ketorolac, nepafenac, and placebo found no difference between the groups in the incidence of postoperative macular edema. In a recent report of the American Academy of Ophthalmology (AAO), the authors rigorously evaluated the current literature on the effectiveness of topical NSAIDs in preventing vision loss from CME after cataract surgery. They concluded that although NSAIDs are effective in reducing the incidence of optical coherence tomography (OCT)-based or angiographic CME and hastening visual recovery in the short term when compared to placebo or topical steroids, there is a lack of level I evidence to suggest that routine prophylactic use of NSAIDs reduces long-term (> 3 months) vision loss from CME after cataract surgery.

**TREATMENT OF PSEUDOPHAKIC MACULAR EDEMA**

NSAIDs are commonly used by retina specialists early in the treatment algorithm for pseudophakic CME (PCME) in combination with topical corticosteroids. Pseudophakic CME can be classified as either acute (occurring < 4 months from surgery) or chronic (occurring > 6 months after surgery). Acute PCME has a peak incidence at 6 weeks postoperatively and often resolves without treatment. Heier et al. compared ketorolac monotherapy, prednisolone monotherapy, and ketorolac/prednisolone combination therapy for the treatment of acute PCME and found that combination therapy offered advantages over monotherapy with either agent. Another study compared diclofenac versus ketorolac monotherapy for acute PCME and found both were equally beneficial. Although these results are encouraging, the study groups were small and the latter study did not include a control group. The authors of a recent Cochrane review concluded that the evidence was insufficient to inform practice, but that there may be a therapeutic benefit especially if combined with topical steroids.

That same Cochrane review uncovered four articles addressing the use of NSAIDs in the treatment of chronic PCME. The first two studies published may be less relevant at this time given they included only aphakic patients’ statuses post-intracapsular cataract extraction. Each found no benefit to treatment with NSAIDs, the first to oral indomethacin and the second to topical fenoprofen. Two randomized, controlled studies by Flach et al. included patients who had undergone intracapsular and extracapsular cataract extraction. Each study included patients with diabetes undergoing cataract surgery and showed early visual acuity benefits. They found no beneficial effect on OCT-based retinal thickening or visual acuity outcomes with 12 months of topical nepafenac compared to placebo. Four years later, these results were confirmed in a larger, multicenter study of 120 patients, which again found an improvement in visual acuity in patients treated with topical ketorolac for 3 months to 4 months compared to placebo. Although there have been several smaller, nonrandomized trials showing the benefit of treatment of chronic PCME with topical NSAIDs, the latter two studies remain the strongest evidence supporting their use for this indication.

**TREATMENT OF DIABETIC MACULAR EDEMA**

Given the fact that patients with diabetic retinopathy have been found to have elevated inflammatory markers and topical nepafenac has been shown to penetrate the retina in animal models, the Diabetic Retinopathy Clinical Research Network (DRCR) designed a randomized, controlled trial evaluating the use of nepafenac for non-center involving diabetic macular edema. They found no beneficial effect on OCT-based retinal thickening or visual acuity outcomes with 12 months of topical nepafenac compared to placebo. A Cochrane review published just prior to the DRCR trial found no other randomized, controlled trials investigating the role of NSAIDs in the treatment of diabetic macular edema. Thus, although nepafenac has been shown to decrease the incidence of postoperative macular edema in patients with diabetic retinopathy, there is currently insufficient evidence to suggest any role for topical NSAIDs in the treatment of diabetic macular edema.
TREATMENT OF UVEITIC MACULAR EDEMA

Although local and systemic steroids remain the standard of care for uveitic macular edema, topical NSAIDs are an attractive alternative given their anti-inflammatory capacity without the unwanted steroid-induced elevation in intraocular pressure. A placebo-controlled, randomized trial of topical 0.5% indomethacin for the treatment of acute, noninfectious uveitic macular edema showed a significant decrease in central subfield thickness on OCT at 6 months compared to placebo. A smaller case series reported a similar beneficial effect of topical nepafenac; however, not all results have been as promising. In a retrospective case series comparing topical bromfenac alone versus in combination with either intravitreal triamcinolone acetonide or bevacizumab (Avastin; Genentech, South San Francisco, CA), topical bromfenac alone had no effect on visual acuity or OCT thickness at 3 months, whereas both combination groups had significant improvement in visual acuity and OCT thickness. Larger randomized, controlled trials are needed to determine the role of NSAIDs in the treatment of uveitic CME.

IMPLICATIONS FOR PRACTICE

In conclusion, the role of NSAIDs in the prevention and treatment of macular edema is evolving. Recent studies suggest that topical nepafenac may play a role in the prevention of macular edema post-cataract surgery in patients with diabetic retinopathy, which supports the popular practice of many cataract surgeons who prescribe topical NSAIDs routinely in diabetic patients undergoing cataract surgery. The use of NSAIDs for the prevention of pseudophakic macular edema in routine cataract surgery remains controversial, and more work is needed in this area. Although the panel responsible for the AAO’s Ophthalmic Technology Assessment (OTA) found insufficient evidence to support their use, some have questioned their decision to use visual acuity at 3 months as their primary outcome. Some studies have suggested that NSAIDs provide more short-term benefits after cataract surgery. Thus, the American Society of Cataract and Refractive Surgeons (ASCRS) suggested that visual outcome at 1 month and patient-reported quality of life would be more appropriate end points as they would better capture any benefit NSAIDs have on hastening visual recovery after cataract surgery, and the ASCRS ultimately did not endorse the OTA report. Pending future work in this area, cataract surgeons need to carefully consider the current evidence and weigh the benefits of treatment in their specific patient population with the additional costs for a limited long-term benefit on visual acuity.

Although the ability of NSAIDs to prevent PCME remains controversial, their role in the treatment of PCME, particularly PCME lasting longer than 6 months in duration, has been shown and confirmed in randomized, controlled trials. There may be added benefit when used in combination with topical steroids, and this should be considered as initial treatment for PCME. Ophthalmologists have been evaluating the role of NSAIDs in the treatment of retinal disease for decades, and future well-designed trials are needed to better define their utility in the treatment and prevention of macular edema, whether alone or in combination with other topical and/or intravitreal therapeutics.

REFERENCES

14. Heier JS, Topping TM, Baumann W, Dirks MS, Chen S. Combination therapy in the treatment of acute pseudophakic cystoid macular


Angela P. Bessette, MD, can be reached at Cole Eye Institute, Cleveland Clinic, 2022 E 105th St, Cleveland, OH 44106; email: angelagpugliese@gmail.com.

Seenu M. Hariprasad, MD, can be reached at the Department of Ophthalmology and Visual Science, University of Chicago, 5841 S. Maryland Avenue, MC2114, Chicago, IL; email: retina@uchicago.edu.

Rishi P. Singh, MD, can be reached at Cole Eye Institute, Cleveland Clinic, 2022 E 105th St, Cleveland, OH 44106; email: drrishisingh@gmail.com.

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