Review of “A randomized trial comparing for preventing cystoid macular edema after cataract surgery” by Jonathan B. Greene, M.D., Scott M. McClinton, M.D., Michael I. Seider, M.D., and Ayman Naseri, M.D.

Because of the importance of evidence-based medicine, every physician must be able to critically appraise clinical studies and the peer-reviewed literature. One of the core competency criteria for residency programs is “practice-based learning and improvement,” meaning that residents should be developing the lifelong skills needed to critically evaluate the published literature. One useful and traditional exercise is the resident “journal club” in which a published study is carefully analyzed with regard to study design, data quality and analysis, clinical implications, and whether the conclusions are supported by the evidence. Every month, a prominent residency program will be selected to review a paper that is scheduled for publication in the concurrent issue of the Journal of Cataract and Refractive Surgery (JCRS). The residency director will coordinate the effort to have a selected group of residents critique the study design and conclusions. The clinical relevance, practicality, and take-home message from the paper will be reviewed. This month, the University of California, San Francisco residents, under program director Ayman Naseri, M.D., kick off this column with their review of a randomized study of post-op inflammatory medications. I hope that these monthly articles highlighting important papers from JCRS will not only help residents but all EyeWorld readers to improve their critical review skills.

David F. Chang, M.D.,
chief medical editor

Cystoid macular edema (CME) remains a common cause of decreased vision following cataract surgery. Given that its pathogenesis is thought to involve the release of inflammatory mediators, anti-inflammatory medications are often used perioperatively for CME prophylaxis. Both topical corticosteroids and non-steroidal anti-inflammatory (NSAID) medications have been used for this purpose; however, the belief that NSAIDs may be more beneficial and offer a more favorable side effect profile has made them an appealing choice.

Miyake et al. designed a double-masked, randomized, interventional study in 59 patients comparing topical 0.1% nepafenac to 0.1% fluorometholone (FML) in preventing CME and blood-aqueous barrier (BAB) disruption up to 5 weeks after small incision cataract surgery. The purpose of the study was to quantify these medications’ impact on CME and BAB function using fluorescein angiography (FA), retinal foveal thickness as measured by OCT, and laser flare-cell photometry, as well as their effect on post-op visual outcome and safety profiles. Analysis demonstrated angiographic CME was present in 14.3% (grade III by Miyake classification in 0.0%) and 81.5% (grade III in 18.5%) in the nepafenac and FML groups, respectively, which was a statistically significant difference. There was a significant increase in foveal thickness on OCT in the FML group compared to the nepafenac group at 2 and 5 weeks post-op. There was significantly less flare in the nepafenac group compared to the FML group. Finally, there was a significant difference favoring the nepafenac group when comparing the percentage of patients with >= 3 levels of logMAR vision improvement from baseline at 5 weeks. Ocular side effects with both medications were mild, and both medications were suggested to be safe. From this data, Miyake et al. concluded that topical nepafenac is more effective than FML in preventing CME and BAB disruption and leads to a more rapid visual recovery rate.

The major study results are supported by well-constructed methods. The investigators avoided several confounders by excluding patients with predisposing features to post-op CME such as use of a prostaglandin, diabetic retinopathy, or history of ocular inflammation. The study was prospective, randomized, and both patients and examiners were blinded to the study group in double-masked fashion to prevent bias. The study quantitatively assessed post-op CME by both the gold standard (FA) and more modern and clinically efficient methods (OCT). Laser flare-cell photometry adds data that more directly evaluate post-op inflammation, a likely contributor to CME. Finally, the analysis utilizes appropriate statistical methods for each data set. Taken together, the conclusions regarding nepafenac and reduction of post-op inflammation and angiographic CME are well supported.

The relationship between nepafenac and visual recovery is not as clear. To support the observation of more rapid visual recovery, the authors separate patients into levels of logMAR improvement. However, they do not report pre- and post-op visual acuities, data critical to contextualize this purported benefit of nepafenac. Similarly, cataract detail, potential comorbidities, and visual potential are not provided beyond baseline lens density information. This forces the reader to assume the two groups were similar in these respects. The relationship between the presence and severity of angiographic CME and improvement in vision was also not included. Evidence suggesting that patients with more CME also had less or slower visual recovery would have made their argument more persuasive. Moreover, patients were only followed post-op for 5 weeks, so persistence of CME and onset of clinical, visually symptomatic CME could not be assessed. In light of these omissions, the reader cannot accurately assess the clinical relevance of nepafenac’s impact on visual acuity or speed of visual recovery.

Other limitations that mitigate the clinical applicability of this study include the choice of FML, a relatively mild steroid with poor intraocular penetration. While this does not affect the authors’ conclusions regarding comparatively decreased inflammation and CME with nepafenac, a stronger topical steroid such as 1% prednisolone acetate may have yielded different outcomes and weakened the statistical

Nepafenac 0.1% versus fluorometholone 0.1% for preventing cystoid macular edema after cataract surgery

Kensaku Miyake, M.D., Ichiro Ota, M.D., Goichiro Miyake, M.D., Hiro Numaga, M.D., Ph.D.

Purpose: To compare a topical nonsteroidal antiinflammatory drug (nepafenac 0.1%) and a topical steroidal antiinflammatory drug (fluorometholone 0.1%) in preventing cystoid macular edema (CME) and blood-aqueous barrier (BAB) disruption after small-incision cataract extraction with foldable intraocular lens (IOL) implantation.

Setting: Shoahzankai Medical Foundation, Miyake Eye Hospital, Nagoya, Japan.

Design: Randomized double-masked single-center clinical trial.

Methods: Patients were randomized to receive nepafenac 0.1% eye drops or fluorometholone 0.1% eye drops 5 weeks after phacoemulsification with foldable IOL implantation. The incidence and severity of CME were evaluated by fluorescein angiography, retinal foveal thickness on optical coherence tomography, and BAB disruption on laser flare-cell photometry.

Results: Thirty patients received nepafenac and 29 patients, fluorometholone. Five weeks postoperatively, the incidence of fluorescein angiographic CME was significantly lower in the nepafenac group (14.3%) than in the fluorometholone group (81.5%) (P<.0001). The fovea was thinnest in the nepafenac group than in the fluorometholone group at 2 weeks (P=.0266) and 5 weeks (P=.0055). At 1, 2, and 5 weeks, anterior chamber flare was significantly less in the nepafenac group than in the fluorometholone group (P<.0001, P<.0001, and P=.0304, respectively). The visual acuity recovery from baseline was significantly greater in the nepafenac group (80.0%) than in the fluorometholone group (55.2%) (P=.0395). There were no serious side effects in either group.

Conclusion: Nepafenac was more effective than fluorometholone in preventing angiographic CME and BAB disruption, and results indicate nepafenac leads to more rapid visual recovery.

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significance of the comparison. For the clinician who currently uses prednisolone acetate or an alternate NSAID for CME prophylaxis, demonstrating the superiority of nepafenac over FML is unlikely to provide clinically relevant information. Additionally, while the extensive exclusion criteria help free the study from confounders, the data generated should not be generalized to these patient populations, many of which are traditionally thought of as higher risk for developing CME and likely to benefit from medical prophylaxis. Finally, it is worth noting that the lead and senior authors are consultants of Alcon (Fort Worth, Texas), the producer of nepafenac, a relationship that may introduce bias.

This study seeks to build on the existing literature by assessing the efficacy of a relatively new topical NSAID as prophylaxis against CME by quantifying CME, intraocular inflammation, and its effect on visual acuity. While multiple studies have demonstrated the efficacy of other topical NSAIDs in reducing the incidence of post-op angiographic CME, the clinical implications of these findings have remained unclear. A recent review by Kim et al. found only one double-masked, randomized, placebo-controlled study demonstrating an improvement in post-op Snellen visual acuity for patients undergoing intracapsular cataract extraction and receiving an older generation topical NSAID (1% indomethacin in sesame oil; preparation no longer available). However, this benefit was not sustained beyond 3 months, and both groups also received corticosteroid medications. Wolf et al. published a retrospective review comparing prednisolone to combination prednisolone and nepafenac when compared to FML. However, the aforementioned limitations prevent it from conclusively demonstrating an impact on vision or superiority to commonly used medications, and these limitations are important as they speak directly to the clinical importance of the study. Further work to elucidate the mechanisms of post-op CME and the prophylactic role of nepafenac and other NSAIDs is needed.

In summary, this study provides compelling evidence that nepafenac reduces post-op intraocular inflammation and angiographic CME when compared to FML. However, the aforementioned limitations prevent it from conclusively demonstrating an impact on vision or superiority to commonly used medications, and these limitations are important as they speak directly to the clinical importance of the study. Further work to elucidate the mechanisms of post-op CME and the prophylactic role of nepafenac and other NSAIDs is needed. EW

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Contact Information
Naseri: aysan.naseri@va.gov

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