when fully tested, safe, and widely available. To the contrary, we encourage their development. Bellini and Brum emphasize the importance of careful incision management, which will not be abrogated when adhesives are generally available.—*Samuel Masket, MD, Shaleen Belani, MD*

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Ketorolac versus nepafenac in cataract surgery

The prospective trial conducted by Duong et al.[1] examining the use of ketorolac 0.4% and nepafenac 0.1% following cataract surgery raises some serious concerns. Several design flaws compromise the integrity of the study and therefore call into question the results. Perhaps most important is that masking was virtually impossible because the 2 test agents had different dosing frequencies (4 times a day for ketorolac and 3 times a day for nepafenac), inviting investigator bias. Moreover, although the authors describe the study as randomized, it appears that the surgical coordinator decided the treatment group of each patient, further biasing the results. In addition, the unconventional practice of switching the colored labeling of the masked groups each month increased the possibility of unintentionally mixing data from the 2 groups.

The planning and justification of the trial were not explained in the text, raising questions about the primary outcome variable, study size and power, and outcome analysis; thus, it is not possible to discern whether this study was adequately designed and powered to support its conclusions. If not, the study must be considered exploratory and the conclusions can be used only for hypothesis generation. While the reasons for using distinct surgical kits (in which each nonsteroidal antiinflammatory drug [NSAID] is paired with a different antibiotic and corticosteroid) and different NSAID dosing frequencies are understandable, these decisions introduce undue variations into the trial design, making it difficult to assign outcome differences solely to the type of NSAID administered. Finally, bias may have been introduced through analgesic use; although the authors do not comment on patient use of analgesics, it is reasonable to assume that some patients would have taken them, thereby confounding the analgesic-related outcomes of the study.

With respect to the outcomes reported, several issues should be raised. First, the authors report a significantly higher posterior capsule opacification (PCO) rate in the nepafenac group, but neglect to describe how they classified PCO with respect to grade and coverage of the posterior capsule. Because PCO is not simply present or absent, but rather is graded on a continuum of severity and extent, the reported percentages provide little information. In addition, the authors fail to address numerous factors that affect PCO rate, including surgical technique (eg, size of capsulorhexis) and relevant patient characteristics such as diabetes mellitus (without diabetic retinopathy) and refractive error.[2] Furthermore, the increased rate of PCO development with nepafenac after only 1 month is not consistent with published literature citing a neutral or a protective effect by NSAIDs on PCO development.[3,4] Thus, factors independent of NSAID treatment were likely responsible for the between-group difference in PCO rate.

The reporting of visual acuity results at day 1 also poses a concern. The numerical advantage of ketorolac 0.4% (0.54 logMAR versus 0.63 logMAR) was described in the text as being "slightly better" than nepafenac. Given the lack of statistical significance, this difference is likely spurious.

Finally, of major concern is the interpretation of the patient-reported outcomes. Aside from the patient questionnaire being administered only on day 1, when responses about compliance cannot be expected to be reliable, the authors overstate the importance of the between-group differences in patient satisfaction, compliance, and pain control. In addition to the already stated concerns regarding compliance and analgesic-related outcomes, further reservations about the results should be noted: The small between-group differences in all 3 of these categories (0.25- to 0.40-point differences on a 5-point scale) with such large standard deviations, while questionably statistically significant, can hardly be considered clinically relevant. Thus, the study conclusion discussing the statistical advantage of ketorolac with respect to patient satisfaction, compliance, and pain control is misleading. A more appropriate conclusion would be "nepafenac 3 times a day and ketorolac 4 times a day were both effective and clinically comparable in anterior segment ophthalmic surgery and patient perception."

In conclusion, when one considers the lack of true masking and randomization, the confounding use of surgical kits, as well as the questionable interpretation of much of the results, the validity of the entire study is called into question.

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REPLY: As stated, the study was double-masked. One ophthalmologist performed the surgery, and 1 ophthalmologist conducted the postoperative evaluation. Neither ophthalmologist was aware of which NSAIDs the patients were instilling. During the study period, the ophthalmic technicians were responsible for ensuring that patients were using the appropriate medications along with proper dosing in the absence of the ophthalmologist; ie, during the history portion of the visit. Before, during, or after the ophthalmic examination, the ophthalmic technician would verbally relay to the ophthalmologist that the patient was instilling the appropriate topical medication with the correct dosing without verbalizing the actual dosing regimen. The evaluating ophthalmologist was instructed not to ask the patient what topical medications he or she was using. The electronic medical record documented the postoperative pharmacological drug class without referencing the name of the NSAID, steroid, antimicrobial, and the dosing regimen. I believe the process used for this study does minimize, if not eliminate, true or potential biases from the examining ophthalmologist even if the dosing frequencies of the medications differ.

Apart from the patients being cleared for cataract surgery, the surgical counselor did not know the patients' medical and ocular histories. When the patient consented to be enrolled in the study, the respective topical medication was given at random; it was not based on financial or social factors, insurance, or demographics. Owing to the frequency with which cataract surgery patients change their minds, become ill, or experience unexpected life-altering events, random distribution was determined to be best. It is valid to question the practice of switching the colored labeling of the masked groups each month; however, a built-in method to prevent mixing the groups was used. In the surgery log generated by the surgery counselor, the respective NSAIDs were recorded along with the color code for the month. The discharging nurse had a list of patients along with the surgery log and next to the patient's name was the appropriate postoperative kit to be given. The red or blue label was used to group the patients so that during the data collection period, the number of patients and the names of patients were correctly matched and recorded.

Posterior capsule opacification is an inherent postoperative complication in cataract surgery. Research, intraocular lens design, surgical techniques, and pharmacotherapy have significantly decreased the incidence of PCO. In this study, the incidence of PCO was high; however, it was clearly stated in the article that the "true" prevalence of PCO could not be determined and further evaluation was needed at 6 and 12 months to assess whether there was a direct correlation between the use of nepafenac and the development of early PCO. In the article, all the points (ie, preoperatively, intraoperatively) potentially associated with the development of PCO were made. In short, what was observed was reported but there was latitude in terms of correlation.

All the study patients were instructed to use their respective medications 3 days before surgery. Before discharge and in addition to the topical steroid, the patients were instructed to continue using their respective preoperative medications until further instructions were given. Along with other indications, both medications were indicated for ocular pain management postoperatively. The survey was given to address pain control in the immediate postoperative period and within the first 48 hours. I agree that in general, surveys are subjective, but I disagree with the comment that we "overstate the importance of the difference . . . ." The subjective nature of the survey was quantified, and the important differences were not overstated. The study simply reported the numeric value. In my opinion, the language used to report the finding was succinct. It was suggested that a more appropriate conclusion would be, "Nepafenac 3 times a day and ketorolac 4 times a day were both effective and clinically comparable in anterior segment ophthalmic surgery and patient perception." The first part of the statement is true and was clearly stated in the first line of the last paragraph in the discussion. The second part, "patient perception," is incorrect. If that statement were made, it would surely contradict the statistical findings.

Finally, the study was conducted at a single-center private practice and no party involved had any financial or proprietary gains. The study was not funded by a company or institution. It was conducted to assess overall patient satisfaction with the respective NSAIDs and potential clinical outcomes. Outcomes from studies will be positive or negative and in the purest definition of the scientific method, this study was conducted ethically and without bias or incentive.—*Hon-Vu Quang Duong, MD, Kenneth C. Westfield, MD, Thomas H. Chalkley, MD*