Prophylactic nepafenac and ketorolac versus placebo in preventing postoperative macular edema after uneventful phacoemulsification

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PURPOSE: To evaluate the efficacy of prophylactic ketorolac 0.5% versus nepafenac 0.1% versus placebo on macular volume 1 month after uneventful phacoemulsification and evaluate the health-related quality-of-life (HRQOL) of topical nonsteroidal antiinflammatory drugs (NSAIDs) in the context of cataract surgery.

SETTING: Hotel Dieu Hospital, Kingston, Ontario, Canada.

DESIGN: Prospective placebo-controlled parallel-assignment double-masked randomized clinical trial.

METHODS: In this study, patients 18 years or older scheduled for routine phacoemulsification were randomized to a placebo, ketorolac 0.5%, or nepafenac 0.1% and dosed 4 times a day starting 1 day before surgery and continuing for 4 weeks. Spectral-domain macular cube ocular coherence tomography scans measuring central subfield thickness, macular cube volume, and average macular cube thickness were performed at baseline and 1 month postoperatively. The HRQOL metrics were determined with the Comparison of Ophthalmic Medications for Tolerability (COMTOL) questionnaire.

RESULTS: Each study group comprised 54 patients. One month postoperatively, although a trend toward significance occurred for nepafenac and ketorolac, analysis of the means of differences showed no statistically significant differences between the 3 study groups ($P = .2901$). The COMTOL analysis found no difference in tolerability, compliance, side-effect frequency and bother, and effects on HRQOL between ketorolac and nepafenac compared with the placebo.

CONCLUSIONS: One month after uneventful phacoemulsification, there was no difference in macular volume between the placebo, ketorolac, and nepafenac. Ketorolac and nepafenac were well tolerated with minimal side-effect profiles. Thus, for patients without risk factors having routine surgery, prophylactic topical NSAIDs are not recommended.

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Cataract extraction is the most commonly performed surgical procedure in the developed world and is frequently associated with postoperative ocular inflammation. Nonsteroidal antiinflammatory drugs (NSAIDs) inhibit the 2 forms of the cyclooxygenase (COX) enzymes, COX-1 and COX-2, and prevent the production of endoperoxides, mainly prostaglandins (eg, G2, COX-H2), and their downstream inflammatory effects.[1–4] Cyclooxygenase inhibition minimizes intraoperative miosis, reduces ocular–blood barrier permeability, reduces conjunctival hyperemia, and minimizes fluctuations in intraocular pressure (IOP).[5] At present, there are 4 available topical NSAID preparations, including the phenylacetic acids diclofenac 0.1%, ketorolac 0.5%, and bromfenac 0.09%. In addition is the arylacetic acid nepafenac 0.1%, which unlike the other topical NSAIDs is not a free acid but rather an NSAID prodrug that crosses the cornea and is bioactivated to the active amfenac moiety by intraocular hydrolases.[6]

There is good evidence that topical NSAIDs are effective at reducing postoperative anterior segment inflammation after cataract surgery without significant

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toxicity.[7–10] However, there is no evidence to suggest that 1 topical NSAID is better than another in controlling postoperative inflammation.[11,12] A more controversial issue surrounds the use of prophylactic NSAIDs to minimize postoperative macular edema after cataract surgery. There is some evidence that combination therapy with ketorolac and corticosteroids may be more effective than corticosteroids alone at preventing and treating cystoid macular edema.[13,14] We previously found that prophylactic ketorolac, in addition to topical corticosteroids, decreased macular volume after cataract surgery.[15] The question remains whether the pro-NSAID nepafenac, with its purported improved ocular penetration, is superior in this context.[9,16]

One major aspect that has been missing in the aforementioned literature is the evaluation of health-related quality-of-life (HRQOL). Although numerous topical NSAID medications are available, little is known about their effect on the HRQOL of patients having cataract surgery. Moreover, because traditional topical NSAIDs are associated with frequent use (4-times-a-day dosing) and have the potential for ocular irritation (eg, patient-reported stinging and burning), an analysis of their tolerability is warranted, especially since nepafenac may offer an improvement by means of its prodrug mechanism of action. The Comparison of Ophthalmic Medications for Tolerability (COMTOL) is a validated questionnaire that was developed for use in clinical trials to compare the tolerability of multiple topical ophthalmic medications and to aid the reporting of spontaneous adverse events.[17]

The current study evaluated the efficacy of prophylactic ketorolac 0.5% versus nepafenac 0.1% versus placebo (in addition to routine topical antibiotic and prednisolone 1.0% drops) in terms of macular volume (assessed by spectral-domain optical coherence tomography [OCT]) 1 month after uneventful phacoemulsification cataract extraction. The COMTOL instrument was used to evaluate the HRQOL and tolerability of prophylactic topical NSAIDs in the context of uneventful cataract surgery. The aim was to evaluate what role, if any, prophylactic NSAID drops have in decreasing macular edema after uneventful cataract surgery.

PATIENTS AND METHODS

Patient Enrollment

This prospective placebo-controlled parallel-assignment double-masked randomized clinical trial was performed at 1 site in Canada (Hotel Dieu Hospital, Kingston, Ontario) from March 2010 to May 2011. The study was approved by the Queen's University Health Science and Affiliated Teaching Hospitals Research Ethics Board and is registered with the National Institutes of Health clinical trials[A] according to the standards set by the International Committee of Medical Journal Editors and the World Health Organization. All patients were treated according to the Declaration of Helsinki document on human research ethics, and all patients underwent a process of informed consent.

Patients 18 years of age or older were enrolled from 2 general ophthalmology clinics if they had a cataract and were expected to have phacoemulsification with implantation of a posterior chamber intraocular lens (IOL). Patients were excluded if they had preexisting retinal disease (eg, diabetic retinopathy, vein occlusion, exudative macular degeneration), previous uveitis, previous intraocular surgery, or an allergy or hypersensitivity to NSAIDs. Enrolled patients who had complicated cataract surgery (eg, significant corneal edema, posterior capsule rupture, vitreous loss, dropped nuclear material, retained cortical material, or an IOL not placed in the capsular bag) were subsequently excluded.

Study Protocol

Patients presenting with cataract who did not have an exclusion criterion were enrolled in a consecutive manner. Information on demographics (birthdate, sex, age), medical history, and ocular history were recorded at the initial visit. The baseline examination included corrected distance visual acuity (CDVA), IOP, slitlamp evaluation, and dilated fundus evaluation. In addition, a baseline OCT macular cube scan was performed before surgery (see below for OCT protocol). Postoperatively, patients were routinely evaluated at day zero or at 1 day as well as at 1 month for study completion. The 1-month visit consisted of CDVA, IOP, slitlamp examination, and an OCT macular cube scan. At any time in the study, patients were evaluated if there were concerns regarding the postoperative course. Complications and adverse events were monitored during the follow-up period.

Patients were randomly assigned to receive a placebo (sterile saline drops), nepafenac 0.1%, or ketorolac 0.5%. The placebo, nepafenac, and ketorolac suspensions were supplied in identical generic drop bottles that were individually made by the Kingston General Hospital Investigational Pharmacy division. Bottles concealed medication information and were labeled with study identification number, patient identification number, expiration date, and emergency contact information only. Patients were instructed to instill 1 drop in the operative eye 4 times a day (breakfast, lunch, dinner, and before bedtime). They began dosing 1 day before

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surgery and continued for 4 weeks. On the day of surgery (day zero), patients were instructed to continue the normal 4-times-a-day dosing of their study drops. In addition, as part of routine care at the institution, patients received gatifloxacin 0.3% drops 4 times a day starting 3 days before surgery and continued for 1 week after surgery. All patients received prednisolone 1% drops (started on day zero) 4 times a day for 1 week, 3 times a day for 1 week, 2 times a day for 1 week, and 1 time a day for 1 week.

All OCT imaging was performed with a spectral-domain Cirrus HD-OCT device (Carl Zeiss Meditec AG). The imaging protocol consisted of the macular cube 512 × 128 program and was performed by experienced staff. The best-quality macular cube images of all scans taken at each visit were chosen and tabulated. Any areas of interest were imaged with the detailed program of the OCT device. All patients received imaging at baseline and at their 1-month follow-up examination. Specifically, central subfield thickness (CST, μm), macular cube volume (VOL, mm^3), and average macular cube thickness (AVG, μm) were collected from each patient for statistical analysis.

All surgeries were performed by 1 of 2 surgeons (S.R.E., T.U.). The surgeries consisted of clear corneal phacoemulsification cataract extraction with in-the-bag IOL placement.

Comparison of Ophthalmic Medications for Tolerability Questionnaire

The COMTOL is an 11-item interview questionnaire developed for use in clinical trials to compare the tolerability of topical ophthalmic medications.[17] It identifies the frequency of side effects (question 4: burning/stinging, redness, blurred vision, bitter taste, unusual taste, itchy eyes, discharge from eyes, swelling of eyelids, brow ache, dimming of vision, difficulty focusing from near to far, dry eyes, trouble reading, trouble seeing at night, tearing) as well as the degree of bother of these side effects (question 5: not at all, a little, some, very much so, extremely so). Moreover, the questionnaire contains questions dealing with the limitations to activities (question 7: driving during the day, driving at night, lifting or carrying groceries, climbing 1 flight of stairs, walking several blocks, reading the newspaper, reading other than the newspaper) and their corresponding degree of bother (question 8: not at all, a little, some, very much so, extremely so).

The COMTOL evaluates HRQOL with 4 global questions. One covers to what extent quality of life is affected by the side effects (question 6; not at all, a little, some, quite a bit, very much so, extremely so). Others cover to what extent quality of life is affected by activity limitations (question 9: not at all, a little, some, quite a bit, very much so, extremely so), how often medications were missed (question 10: I did not miss any doses, rarely, a few times, fairly often, usually, almost always, always), and how satisfied the patients were with the medications (question 11: totally satisfied, very satisfied, somewhat satisfied, somewhat dissatisfied, very dissatisfied, totally dissatisfied).

In this study, patients were interviewed after the 1-month postoperative examination was completed. The aim was to capture the frequency and bother of common side effects and measure the extent to which these side effects limit routine living activities or interfere with HRQOL, medication compliance, and patient satisfaction with the medication. The COMTOL questionnaire has good to excellent internal consistency (0.73 to 0.98), reliability (0.76 to 0.94), and reproducibility (0.75 to 0.93).[17] Although the COMTOL instrument was originally developed for comparing topical ophthalmic medications used in glaucoma clinical trials, it was decided that it would be an appropriate instrument for topical NSAIDs given their common association with similar side effects (eg, burning/stinging, redness, blurred vision). More important, because the COMTOL has acceptable characteristics for inclusion as a tolerability measure, it provides the necessary HRQOL metrics that would aid the full evaluation of the benefits and drawbacks of ketorolac and nepafenac topical therapy in the context of cataract surgery.

Main Outcome Measures and Study Endpoints

The main outcome measure was the change in OCT macular cube CST, VOL, and AVG at 1 month. The secondary outcome measure was the COMTOL HRQOL analysis. Patients who received the study drugs, completed surgery, and completed the follow-up were included in the intent-to-treat analyses. All patients who received the study drugs were included in the safety analysis. Adverse events were documented when solicited from study patients or reported by investigators. An adverse event was defined as any unfavorable, unintended sign, symptom, or clinical result associated with the study drugs. The COMTOL instrument can capture any missed adverse events and side effects and was used as part of the safety analysis.

Statistical Analysis

Sample size was calculated from the observed difference and pooled standard deviation (SD) from a previous study of ketorolac with the sensitivity to detect a 45% reduction in macular volume.[15] A 45% reduction in macular volume was considered to be clinically significant and thus defined the threshold for the ability to detect a significant difference. A power of 80% and confidence level of 95% yielded a sample size of 45 patients per arm. However, because 2 tests were being performed (ie, 2 NSAIDs against 1 placebo), to ensure the overall test was significant, each test had to be significant. This was treated with Bonferroni correction, which errs on the side of larger sample size for multiple comparisons, to yield a final sample size of 54 per arm for a total of 162 participants. Comparisons between 1 month and baseline for CST, VOL, and AVG were performed with paired *t* tests. The COMTOL analysis between groups was performed with the Fisher exact test.

RESULTS

Of the 193 patients enrolled, 162 completed the study. Investigators withdrew 3 patients from the study because they had an intraoperative broken posterior capsule. Two patients had surgery rescheduled outside the study period. In addition, 17 patients (7 placebo, 6 ketorolac, 4 nepafenac) withdrew voluntarily because they were unable to keep their 1-month follow-up appointment. Seven patients (3 placebo, 2 ketorolac, 2 nepafenac) withdrew, stating the 4-times-a-day drops were too onerous to continue until completion. One patient in the ketorolac group was hospitalized with a cardiovascular event and could not complete the follow-up. Finally, 1 patient on nepafenac

had side effects of ocular redness and irritation and could not continue with the study. No postoperative OCT data were collected for patients who did not complete the study. No patients were lost to follow-up.

One hundred sixty-two patients, 54 in each arm, made up the intent-to-treat data set. The mean age was 72.4 years ± 8.2 SD (range 50 to 88 years); 88 (54%) were women. There were no differences in age, sex, or operative eye between the 3 groups.

All 3 groups had varying statistically significant intragroup differences between 1 month and baseline for the OCT variables. At 1 month, the VOL increased by 0.76 mm^3 in the placebo group ($P < .0001$), by 0.43 mm^3 in the ketorolac group ($P = .0085$), and by 0.48 mm^3 in the nepafenac group ($P < .0001$). Similarly, the AVG increased by 21.2 μm ($P < .0001$), 10.3 μm ($P = .0398$), and 12.9 μm ($P < .0001$) in the placebo, ketorolac, and nepafenac groups, respectively. For the CST at 1 month, there was an increase of 17.1 μm ($P < .0001$) in the placebo group. In contrast, there was no significant increase in the CST in the ketorolac group (14.5 μm; $P = .0578$) or the nepafenac group (10.2 μm; $P = .0578$).

The VOL was statistically significantly greater in women than in men ($P = .023$). Sex did not have a significant effect on the other variables at a 5% significance level, and age had no effect at the 5% level. One month after surgery, there was a significant difference in the mean VOL between ketorolac (9.86 mm^3) and nepafenac (10.16 mm^3) ($P = .0491$, the Tukey honestly significant difference test); however, there was no significant difference between either medication and the placebo (10.07 mm^3).

There were no statistically significant differences in the means of differences in the CST, VOL, and AVG values between the 3 study groups at 1 month. For VOL, the means of the differences between 1 month and baseline were significantly lower in the ketorolac group (0.43 ± 1.16 mm^3) and the nepafenac group (0.48 ± 0.72 mm^3) than in the placebo group (0.76 ± 1.27 mm^3); however, the differences were small compared with the SDs and were not statistically significant ($P = .2901$). In other words, at 1 month, the VOL was 0.43 mm^3 and 0.48 mm^3 larger than at baseline in the ketorolac group and nepafenac group, respectively, while it was more elevated (0.76 mm^3) in the placebo group.

In the boxplots of VOL values, three quarters of the observations in each group are tightly aligned, showing there was little difference in VOL between the groups for three quarters of the data (Figure 1, *top*). The ketorolac group had mean values very close to the first quartile, with even larger drops in VOL values outside the three quarters of data, while nepafenac produced a more uniform response with fewer outliers. Ketorolac lowered postoperative VOL values beyond baseline in many patients, and the median was below

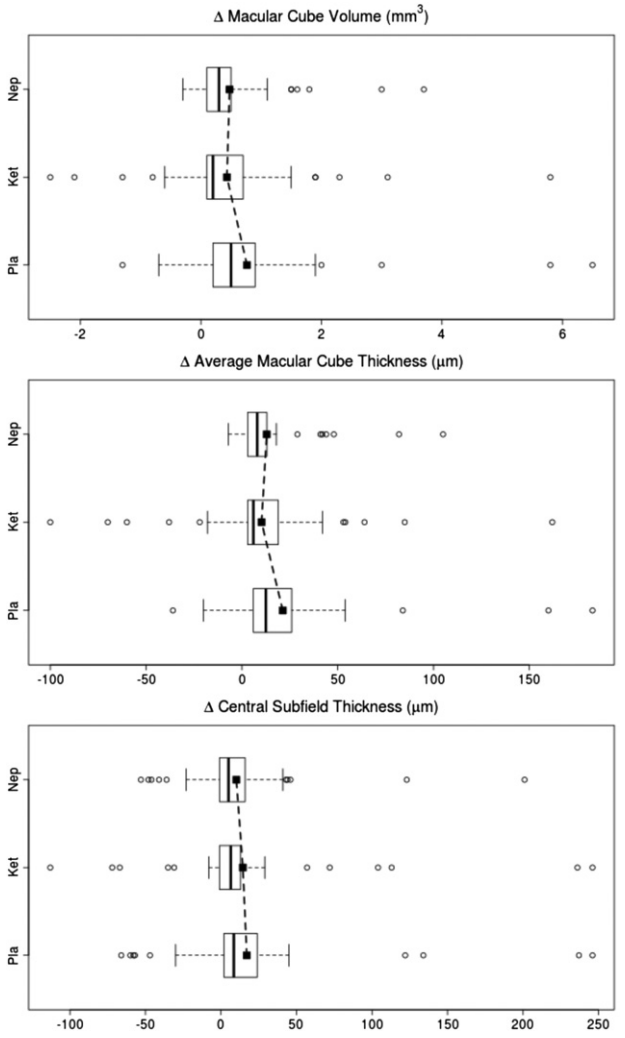

Figure 1. Differences between 1 month and baseline for OCT cube values. The area of the box represents three quarters of the data, and the small circles beyond the whiskers represent outliers; outliers are defined as greater than 1.5 times the interquartile range beyond the hinge (the nearest of the first or third quantile). The line in the center of the box represents the median, and the black box represents the mean; the dashed black line connects the means.

the mean in all cases (Figure 1, *top*). In contrast, nepafenac did not produce large changes in the VOL and retained a tight distribution of postoperative values.

At 1 month, there was no statistically significant difference in means of difference in AVG (Figure 1, *middle*) or CST (Figure 1, *bottom*) between the 3 groups. Similarly to the VOL, there were large outliers with lower values in the ketorolac group than in the nepafenac group; however, this was not significant compared with the placebo group. In all cases, the differences between the 3 groups were small and not statistically significant. The total effect size for ketorolac and nepafenac, when compared with the placebo, was approximately 31% of the SD, which was very small and not statistically significant.

For the study as a whole group, at 1 month, the CDVA improved by 0.24 logMAR ($P<.001$); however, there was no difference in means ($P=.3551$) or ranked means ($P=.5743$) between the placebo group (-0.22 ± 0.23 logMAR), the ketorolac group (-0.22 ± 0.23 logMAR), or the nepafenac group (-0.27 ± 0.21 logMAR). The IOP decreased by 0.93 mm Hg ($P<.001$) at 1 month with no difference in means ($P=.2857$) or ranked means ($P=.5743$) between the placebo group (1.4 ± 2.5 mm Hg), the ketorolac group (0.7 ± 2.5 mm Hg), or the nepafenac group (0.7 ± 3.8 mm Hg). There were no cases of IOP measurements above 30 mm Hg and no complications related to IOP; the highest IOP at 1 month was 26 mm Hg.

Ninety-seven patients (35 placebo, 32 ketorolac, 30 nepafenac) completed the COMTOL interview questionnaire (60.0% response rate). Sixty-five patients declined the COMTOL telephone interview after surgery for logistical reasons, such as time requirements to complete the interview. Patients who initially declined to complete the COMTOL were called 3 times at mutually determined, convenient times; if they declined the third time, they were excluded from the COMTOL analysis.

Figure 2 shows the frequency of side effects (COMTOL question 4). There was no significant between-group difference in the frequency of side effects between "I did not have the symptom" and any greater frequency (question 4; $P=.7729$). For degree of bother from these side effects, there was no significant difference between "not at all" and any reported bother (question 5; $P=.7302$). Similarly, there was no significant between-group difference in limitations to activities secondary to side effects (question 7; $P=.9978$) or degree of bother from side effects between "not at all" and any reported bother (question 8; $P=.9824$).

The global HRQOL questions showed no difference in the extent to which quality of life was affected by medication side effects between "not at all" and any reported effect (question 6; $P=.8476$). Regarding the extent quality of life was affected by activity limitations, there was no difference between "not at all" and any reported limitations (question 9; $P=.8584$). According to the COMTOL questionnaire, there was no difference in compliance between the 3 study groups (question 10; $P=.3801$). Most patients in all 3 groups reported being satisfied with the medication, and there was no difference between satisfied responses and dissatisfied responses (question 11; $P=.4777$).

DISCUSSION

One month after uneventful phacoemulsification cataract extraction, there was no difference in macular volume between a placebo, ketorolac, and nepafenac. Although intragroup differences showed that ketorolac and nepafenac were effective at minimizing increases in the CST and there was an overall trend toward significance, the differences were small and not significant when compared with the placebo. Similarly, although ketorolac appeared to have greater efficacy than nepafenac at lowering total cube volume at 1 month (9.86 mm^3 versus 10.16 mm^3, respectively), there was no significant difference between either medication and the placebo (10.07 mm^3).

We detected subtle differences in the clinical profiles of ketorolac and nepafenac. Ketorolac has the ability to largely reduce macular volume, albeit not consistently and not uniformly. Ketorolac was closer to the primary quartile for lower values in macular volume, and there was a trend toward lower values after surgery. Nepafenac, on the other hand, seemed to lower macular volume to a lesser extent but provided a more consistent response across all patients.

These differing clinical profiles may be explained pharmacologically because ketorolac and nepafenac have different mechanisms of action. Ketorolac is delivered as an active phenylacetic acid that must be absorbed across the cornea to exert an intraocular effect.

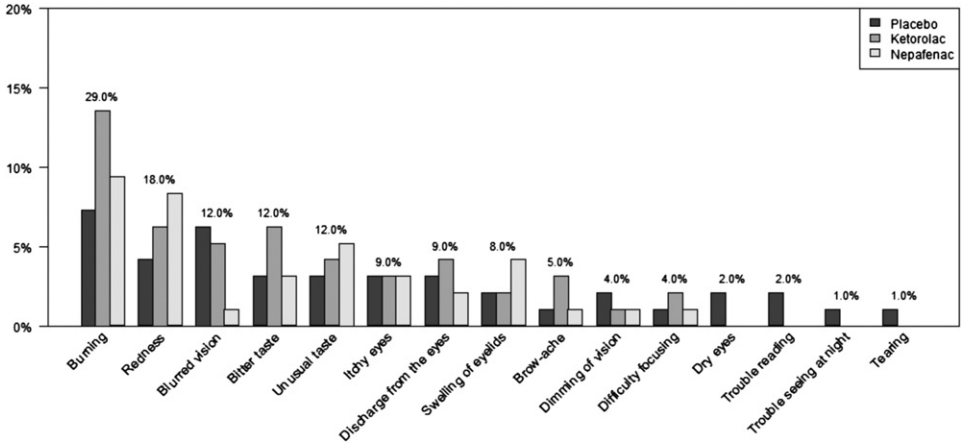

Figure 2. Side-effect symptom and frequency for placebo, ketorolac, and nepafenac described by the COMTOL instrument. The figure at the top of the 3 adjacent bars indicates the percentage of people who experienced the side effect regardless of which drops they used because there was no statistically significant difference between the 3 groups for all side effects.

Nepafenac, an arylacetic acid, is absorbed as a pro-NSAID and is bioactivated by intraocular hydrolases. One would expect nepafenac to be able to rapidly cross the cornea and penetrate the anterior segment better than typical topical NSAIDs, and this is indeed the case.[6] What we could be witnessing is the ability of nepafenac to be readily absorbed by most patients, leading to a very consistent and uniform response. In contrast, ketorolac is able to deliver very large drops in macular volume but does it in a less predictable fashion, possibly because of patient differences in absorption from the ocular surface. It is their differing pharmacology that may be responsible for their clinical response profile; unfortunately, our study was not designed to evaluate pharmacokinetics or pharmacodynamics as part of our large clinical design construct; thus, we can comment on this only indirectly.

We previously found that compared with no treatment, ketorolac significantly decreased macular volume after cataract surgery.[15] Our previous study evaluated a significant number of patients with uveitis, diabetes with and without diabetic retinopathy, hypertension, or macular disease. In our current study, we set out to specifically address low-risk patients with uneventful cataract surgery. There were different pharmacotherapeutic responses in the 2 clinical trials that are likely a function of the patient population. From our cumulative data, when one considers routine uneventful cataract surgery, we make no recommendation for the prophylactic use of topical ketorolac or nepafenac based on their efficacy in lowering macular edema after surgery. The recommendation remains that for at-risk patients (eg, those with diabetes, retinal disease, complicated cataract surgery), prophylactic use of topical NSAIDs is an efficacious and safe intervention to minimize postoperative macular edema. Clinically, we believe the data to be useful because they allow us to counsel patients and discuss the need for additional interventions when having cataract surgery. In this regard, we further define the evolving spectrum of NSAID efficacy in cataract surgery.

The Nepafenac European Registration Study, one of the largest studies comparing ketorolac and nepafenac after cataract surgery, found that nepafenac is equal to ketorolac for the treatment of anterior segment ocular inflammation after cataract surgery.[B] This study did attempt to assess macular volume but relied on dilated fundus assessment rather than OCT to grade macular edema; OCT is now the standard for quantitative macular assessment. As such, the authors could make no conclusions regarding the use of nepafenac and ketorolac for macular edema after cataract surgery. In light of current OCT-imaging technology, spectral-domain OCT continues to be a powerful modality in the armamentarium of the cataract surgeon to monitor patients closely after cataract surgery.

In our study, ocular adverse events were not serious, were mostly mild in intensity, and generally resolved without additional treatment. The incidence of ocular adverse events was similar in patients receiving ketorolac or nepafenac and those receiving the placebo. In fact, there were no limitations on activities and no effect on HRQOL between ketorolac and nepafenac versus placebo. This supports very good tolerability of topical nepafenac and ketorolac in cases of uneventful cataract surgery. Although nepafenac is purported to be better tolerated because of its pro-NSAID chemical structure, we could find no difference between it and ketorolac using the COMTOL instrument. Both drops were tolerated well with few patient complaints.

In conclusion, we found no difference between ketorolac 0.5% and nepafenac 0.1% versus a placebo in decreasing macular edema after uneventful cataract surgery. Both topical NSAID medications had excellent tolerability and acceptable side-effect profiles with no negative effect on HRQOL. When considering the evolving spectrum of NSAID use in cataract surgery, for patients having routine phacoemulsification cataract extraction with no risk factors for macular edema and no intraoperative complications, we do not recommend prophylactic use of topical NSAIDs.

WHAT WAS KNOWN

- Topical NSAIDs are commonly used perioperatively during phacoemulsification but their prophylactic effect on postoperative macular edema after routine cataract surgery is unclear.
- The tolerability and HRQOL of topical NSAIDs in the context of routine phacoemulsification cataract surgery has not been evaluated.

WHAT THIS PAPER ADDS

- In low-risk patients with uneventful cataract surgery, prophylactic use of topical ketorolac or nepafenac seems to offer no benefit in preventing OCT changes indicative of macular edema after surgery.
- Topical NSAIDs are well tolerated with ocular adverse events that are not serious, are mostly mild in intensity, and generally resolve without additional treatment.
- When considering the evolving spectrum of NSAID use in cataract surgery, for patients having routine phacoemulsification with no risk factors for macular edema and no intraoperative complications, there may not be a significant benefit associated with the prophylactic use of topical NSAIDs.

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