Ketorolac tromethamine LS 0.4% versus nepafenac 0.1% in patients having cataract surgery

Prospective randomized double-masked clinical trial

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PURPOSE: To compare the clinical, subjective, and objective outcomes of the use of 2 topical nonsteroidal antiinflammatory drugs—ketorolac tromethamine LS 0.4% (Acular) and nepafenac 0.1% (Nevanac)—in patients having cataract surgery.

SETTING: Single-center private practice, Las Vegas, Nevada, USA.

METHODS: One hundred eighty-three patients (193 eyes) with visually significant cataract were recruited for the study. Consenting patients were randomized to a standard regimen of Acular, gatifloxacin 0.3% (Zymar), and prednisolone acetate 1% (Pred Forte) (ketorolac group) or Nevanac, moxifloxacin hydrochloride 0.5% (Vigamox), and prednisolone acetate (Econopred) (nepafenac group). Analysis included subjective complaints (burning, itching, foreign-body sensation, pain level after surgery) and objective findings (visual function, degree of inflammation in the anterior segment, complications).

RESULTS: The ketorolac group consisted of 94 patients (100 eyes) and the nepafenac group, 89 patients (93 eyes). The between-group differences in visual outcomes and anterior chamber inflammation were not statistically significant (mean $P = .33$). There was a higher incidence of posterior capsule opacification in the nepafenac group ($P = 0.019$). Patient satisfaction, patient compliance, and postoperative pain control were statistically significantly better in the ketorolac group ($P = .022$, $P = .023$, and $P = .025$, respectively).

CONCLUSION: Ketorolac tromethamine was statistically significantly better than nepafenac in terms of patient satisfaction, compliance, and postoperative pain control.

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Ketorolac tromethamine and nepafenac are topical nonsteroidal antiinflammatory drugs (NSAIDs) that have been approved by the U.S. Food and Drug Administration (FDA). Ketorolac tromethamine is used in the management of ocular pain, postoperative pain, and intraocular inflammation.[1,2] Nepafenac, a newer topical agent, is indicated for the treatment of pain and inflammation associated with cataract surgery.[3–5] Although both drugs are reported to be efficacious in managing pain and postoperative inflammation after cataract surgery, they differ structurally and pharmacologically. One significant biochemical difference is that nepafenac is a prodrug that possesses both antiinflammatory and analgesic properties; it penetrates the cornea and is hydrolyzed to the active metabolite amfenac. The active metabolite is believed to inhibit the action of prostaglandin H synthase, an enzyme required for prostaglandin production.[6] Ketorolac tromethamine is not a prodrug and exerts its metabolic activity by interfering with the activity of cyclooxygenase 1, inhibiting prostaglandin biosynthesis.[7,8]

The purpose of this comparative study was to determine whether ketorolac tromethamine LS 0.4% (Acular) or nepafenac 0.1% (Nevanac) is better tolerated by patients and which results in less postoperative inflammation, fewer complications, or both.

PATIENTS AND METHODS

This comparative prospective double-masked clinical trial comprised 183 patients (193 eyes) with visually significant cataract. Exclusion criteria were a history of allergic reaction to topical NSAIDs; history of corneal thinning, erosion, ulcer, or perforation; severe proliferative diabetic retinopathy; absolute glaucoma; and age-related macular degeneration (ARMD) with choroidal neovascular membrane. The study,

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which began in December 2005 and ended in April 2006, was approved by the institutional review board.

Drug Randomization and Regimen

After patients were informed of the study's purpose and provided informed consent, they were randomized to receive Acular (ketorolac group) or Nevanac (nepafenac group). Patients who had bilateral surgery were independently randomized to 1 of the 2 groups. Except for the instruction sheet for dispensing the medication, all labels were removed from the medication bottles. Patients were instructed to instill the respective medication in the eye to have surgery for 3 days preoperatively according to the recommended regimen as follows: ketorolac tromethamine, 1 drop 4 times a day and nepafenac, 1 drop 3 times a day. All patients were told to continue with the regimen for 7 days after surgery. In addition, patients received the standard post-cataract surgery regimen of an antimicrobial agent (gatifloxacin 0.3% [Zymar], ketorolac group; moxifloxacin hydrochloride 0.5% [Vigamox], nepafenac group) 4 times a day for 7 days and a topical steroid agent (prednisolone acetate 1% [Pred Forte], ketorolac group; prednisolone acetate [Econopred], nepafenac group) 4 times a day for 7 days and tapered thereafter. The tapering regimen for both steroids was as follows: 3 times a day for 3 days, twice a day for 3 days, every day for 3 days, then discontinued completely.

If a patient met the criteria and consent was given, his or her operative chart was labeled "blue" for the ketorolac group and "red" for the nepafenac group. Only the surgical counselor knew this code. Based on the code, the patient was given the appropriate postoperative surgical pack by the discharging nurse. The codes were changed on a monthly basis to remove the potential for discovery or bias by the surgeon or evaluating ophthalmologist. After the 1-month postoperative evaluation, the records and evaluations were given to the authors for data collection and interpretation. The code was broken, and the patients were placed in their respective study groups.

Surgical Technique

All cataract surgeries were performed at the same ambulatory surgical center by the same surgeon (K.C.W.) using topical anesthesia comprising tetracaine hydrochloride 0.5%; intracameral lidocaine 4% was also given if needed. After cataract extraction by the phaco-chop technique with bimanual irrigation/aspiration, an SI40 intraocular lens (IOL) (AMO) was implanted.

Patient Evaluation

All postoperative evaluations were performed by the same ophthalmologist (T.H.F.C). The numerical grade of the degree of anterior chamber inflammation assigned by the ophthalmologist was used for statistical analysis (ie, +1 cell was given a score of 1; 1 to 2+ cells was given a score of 1.5).

The data collected, interpreted by 1 ophthalmologist (H.V.Q.D.), included medical and ocular comorbidities, intraocular pressure (IOP) by applanation tonometry, dilated fundus examination, and best corrected visual acuity (BCVA). Early Treatment of Diabetic Retinopathy Study visual acuity values were converted into logMAR values for statistical analysis. Data were collected 1 day, 1 week, and 1 month postoperatively.

Patient Questionnaire

Patients were given a questionnaire (Figure 1) 1 day postoperatively. It had 12 questions that were later grouped into 5 categories: preoperative pain/discomfort (questions 1 to 4); postoperative pain control (question 5); subjective complaints of photophobia, crusting, and foreign-body sensation (questions 6 to 9); compliance (questions 10 and 11); and patient satisfaction (question 12). Nine questions were graded on a scale of 1 to 5, with 5 being the most severe. Three questions (10 to 12) were answered "yes," "no," or "occasionally"; each was assigned a numerical value (yes = 5; occasionally = 3; no = 1). The values given were summed and divided by the respective number of eyes.

Patients were asked to write their name on the questionnaire. The names were later cross-referenced to the list that told to which group the patient belonged.

Statistical Analysis

Results were recorded as means ± SD. A P value less than 0.05 was considered statistically significant. The Student t test was used to assess variable differences between the 2 groups. The Fisher exact and chi-square tests were used to test for independence between variables.

RESULTS

Five patients (2 ketorolac group, 3 nepafenac group) and 5 eyes (2 and 3, respectively) were lost to follow-up. Ten patients (6 ketorolac group, 4 nepafenac group) had both eyes operated on during the study period. Table 1 shows the demographics of the patients who remained in the study.

Preexisting Ocular Comorbidities

Preexisting ocular comorbidities in the ketorolac group included primary open-angle glaucoma (POAG) and ocular hypertension (n = 15), ARMD (n = 32), background diabetic retinopathy (n = 4), central retinal vein occlusion (n = 1), and branch

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Allergan and Alcon supplied the clinic with samples of their respective products and provided postoperative surgical packs for all patients.

The staff members and ophthalmic technicians at the Westfield Eye Center and nurses at the American Surgery Center provided assistance throughout the study period.

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Postoperative Patient Questionnaire

All symptoms are graded on a scale from 1 to 5, with 5 being the most severe or intolerable. Please circle the number that best describes each question.

Grade

- 1. No symptoms—no subjective complaints
- 2. Minimal
- 3. Mild
- 4. Moderate
- 5. Severe

1. After instilling the medication, did you experience a foreign-body sensation in the eye? (Did the eye feel gritty as though you have sand in it?)	1	2	3	4	5
2. After instilling the medication, did you experience a sticky sensation—a sensation like 2 eyelids sticking together or the eyelid sticking to your eye?	1	2	3	4	5
3. After instilling the medication, did you experience any itching?	1	2	3	4	5
4. After instilling the medication, did you experience any pain?	1	2	3	4	5
5. Notwithstanding the pain from the medication, grade the pain level the day after surgery.	1	2	3	4	5
6. After instilling the medication, did you experience any burning sensation?	1	2	3	4	5
7. After instilling the medication, did you experience tearing?	1	2	3	4	5
8. After instilling the medication, did you experience sensitivity to light?	1	2	3	4	5
9. After instilling the medication, did you experience any eye discomfort?	1	2	3	4	5
10. Did you have difficulty putting the medication into your eye?	Yes		Occasionally		No
11. Did you use the prescribed medication as instructed?	Yes		Occasionally		No
12. Were you satisfied with the medication?	Yes		Occasionally		No

Figure 1. Patient questionnaire.

retinal vein occlusion (BRVO) (n = 1). Other comorbidities included ectropion, entropion, pseudohole, and dry eye. Medical comorbidities included hypertension; diabetes mellitus II; hypercholesteremia; coronary artery disease; peripheral vascular disease; and breast, lung, and prostate cancer.

Preexisting ocular comorbidities in the nepafenac 0.1% group included POAG and ocular hypertension (n = 11), ARMD (n = 42), background diabetic retinopathy (n = 5), macular scar (n = 2), and BRVO (n = 1). Other comorbidities included dermatochalasis, entropion, and dry eye. Medical comorbidities included hypertension, diabetes mellitus II, hypercholesteremia, coronary artery disease, heart disease, thyroid disease, and breast and lung cancer.

Table 1. Patient demographics.

	Group	
Demographic	Ketorolac	Nepafenac
Patients, n	92	86
Eyes, n	98	90
Sex, n (%)		
Male	41 (44.57)	39 (45.35)
Female	51 (55.43)	47 (54.65)
Age, y		
Mean ± SD	68.92 ± 12.18	69.47 ± 10.67
Range	44–86	41–83

Visual Outcomes

Figure 2 shows the preoperative and postoperative logMAR BCVA. The mean baseline visual acuity was 0.70 ± 0.67 (20/100 Snellen equivalent) (range 20/25 to counting fingers at 6 inches) in the ketorolac group and 0.58 ± 0.65 ($20/70^{-3}$) (range 20/30 to light perception) in the nepafenac group. The difference between groups was not statistically clinically significant; however, clinically, visual recovery in the ketorolac group (0.54) was slightly better than in the nepafenac group (0.63) 1 day postoperatively. The visual acuities at 1 week and 1 month were comparable between groups ($P = .66$ and $P = .16$, respectively). Comparison of the visual outcomes in patients with ocular comorbidity (eg, ARMD, background diabetic retinopathy) and patients without ocular comorbidity was similar between the ketorolac group and nepafenac group ($P = .61$).

Anterior Chamber Inflammation

The anterior chamber inflammation grade in all patients ranged from 0.15 to 0.57 (Table 2). There was no statistically significant difference between the ketorolac group and the nepafenac group (mean $P > .05$).

Posterior Capsule Opacification

There were 5 cases (5.1%) of posterior capsule opacification (PCO) in the ketorolac group and 13 cases (14.4%) in the nepafenac group; the difference between groups was statistically significant ($P = .019$, Fischer

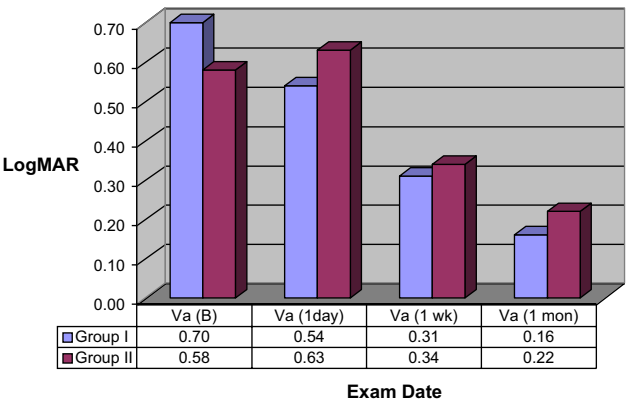

Figure 2. Visual acuity (Va) preoperatively (VaB) and 1 day, 1 week, and 1 month postoperatively (Group I = ketorolac; Group II = nepafenac).

Table 2. Mean postoperative anterior chamber inflammation grade.

Group	Mean at 1 Day	*P* Value	Mean at 7 Days	*P* Value	Mean at 1 Month	*P* Value
Ketorolac	1.09 ± 0.79	.14	0.08 ± .024	.49	0.01 ± 0.05	.48
Nepafenac	0.92 ± 0.77		0.11 ± 0.36		0.02 ± 0.13	

Means ± SD

exact test). Capsule fibrosis was not noted on clinical examination before cataract surgery. Postoperative clinical examination showed development of PCO as early as day 7 in 3 patients in the nepafenac group.

Patient Questionnaire

Patients in both groups had comparable subjective complaints ($P = .13$) and preoperative pain and discomfort ($P = .14$) (Table 3). The ketorolac group had significantly better pain control than the nepafenac group ($P = .025$). Patients in the ketorolac group were significantly more satisfied ($P = .022$) and more compliant than patients in the nepafenac group ($P = .023$).

DISCUSSION

In this study, we evaluated the subjective and objective clinical outcomes between 2 FDA-approved topical NSAIDs, ketorolac tromethamine LS 0.4% and nepafenac 0.1%, in patients who had cataract extraction. The objective data collected included visual acuity, IOP, degree of anterior chamber inflammation, and potential postoperative complications. The subjective data were collected in the form of a questionnaire on preoperative and postoperative pain and discomfort, subjective complaints, and overall patient satisfaction and compliance.

Each patient was given the appropriate postoperative kit that included an antimicrobial agent, topical steroid agent, topical NSAID, and artificial tears. Gatifloxacin and moxifloxacin are bactericidal and have been reported in the literature to have good anterior chamber penetration[9] efficacious against gram-positive and gram-negative organisms and in inhibiting pathogens that cause postoperative endophthalmitis.[10] No significant difference in visual outcomes with either antimicrobial has been reported.[11] Topical steroids have been shown to effectively decrease anterior chamber inflammation.[12,13] The inherent properties and efficacies of the antimicrobial and topical steroid agents are not determining factors in the efficacy of the topical NSAIDs.[14]

Table 3. Results of patient questionnaire.

Category	Mean Score ± SD		*P* Value
	Ketorolac Group	Nepafenac Group	
Postop pain	1.24 ± 0.52	1.49 ± 0.95	.025
Compliance	4.71 ± 0.96	4.31 ± 1.41	.023
Patient satisfaction	4.60 ± 0.86	4.24 ± 1.26	.022
Subjective complaints	1.39 ± 0.68	1.56 ± 0.83	.13
Preop pain/discomfort	1.27 ± 0.62	1.42 ± 0.76	.14

Visual outcomes (acuity and function) were comparable and not statistically significant between groups. Clinically, patients in the ketorolac group appeared to have slightly better visual recovery than patients in the nepafenac group 1 day postoperatively. Statistically, however, the correlation between visual recovery and the NSAIDs was moderately weak.

Postoperative anterior chamber inflammation was well controlled by both topical NSAIDs. Patients were placed on the NSAID, along with the topical antimicrobial and steroid agents, 3 days before surgery and postoperatively. The concurrent use of a topical NSAID and steroid has been shown to significantly decrease anterior chamber inflammation.[15]

The incidence of PCO in the nepafenac group was higher than expected. Although the correlation between the development of PCO and nepafenac was uncertain, it was statistically significant ($P < .05$). The migration of lens epithelial cells,[16,17] diameter of the capsulorhexis,[18,19] chemical[20–22] and physical[23–25] properties of the IOL, and other theories have been implicated in the development of PCO. No patients with PCO had signs of preoperative capsule fibrosis or posterior capsule cataract. Furthermore, there was no evidence of intraoperative complications (capsule tear or retained cortical materials) or postoperative complications, nor did the medical or ocular history presume the development of early PCO. All patients had implantation of an SI40 IOL, and none had capsule polishing. We do not believe the incidence of PCO was related to differing capsulorhexis diameter because the same surgeon performed all procedures. It would be of interest to further evaluate the incidence of PCO in both groups 6 months and 1 year after cataract surgery.

Patient satisfaction is a high priority for any medical practice and especially important for surgical patients.

Pain control is also important to patients. Preoperative pain, discomfort, and other subjective complaints were minimal in both groups. Both topical NSAIDs were well tolerated with few postoperative side effects. Pain control, patient compliance, and satisfaction were better in the ketorolac group than in the nepafenac group.

In conclusion, visual recovery, anterior chamber inflammation, and subjective side effects were statistically similar between the ketorolac group and the nepafenac group. There was a statistically significant higher incidence of PCO in the nepafenac group. Statistically, the data indicate that ketorolac was slightly better in terms of patient compliance, satisfaction, and postoperative pain control. The higher incidence of PCO in the nepafenac group is a compelling factor, suggesting the necessity of a follow-up study with the same patients 6 and 12 months after surgery to determine whether there was a direct correlation between the development of PCO and the use of nepafenac.

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