Effect of topical ketorolac 0.4%, nepafenac 0.1%, and bromfenac 0.09% on postoperative inflammation using laser flare photometry in patients having phacoemulsification

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PURPOSE: To study the effect of topical ketorolac 0.4% (Acular LS), bromfenac 0.09% (Megabrom), and nepafenac 0.1% (Nevanac) on postoperative inflammation using laser flare photometry in patients having phacoemulsification with posterior chamber intraocular lens (PC IOL) implantation.

SETTING: Tertiary care center, Chandigarh, India.

DESIGN: Prospective randomized case series.

METHODS: Patients with age-related cataract having phacoemulsification with PC IOL implantation were randomized into 4 groups receiving topical ketorolac 0.4% (Group A), bromfenac 0.09% (Group B), nepafenac 0.1% (Group C), or no nonsteroidal antiinflammatory drugs (NSAIDs) (Group D, control). The topical NSAIDs were started 1 day prior to the surgery and continued for 6 weeks postoperatively. All patients received a standard regimen of moxifloxacin 0.5% (Vigamox) and prednisolone acetate 1.0% (Pred Forte) eyedrops in tapering doses postoperatively. Visual acuity, intraocular pressure (IOP), laser flare photometry, and fundus examination were done preoperatively and postoperatively at 1 day and 1, 2, 4, and 8 weeks.

RESULTS: The study comprised 120 patients (120 eyes) (Group A = 33 patients, Group B = 30 patients, Group C = 31 patients, and Group D = 26 patients). The laser flare photometry values at the end of 4 weeks and 8 weeks were minimal in the nepafenac group compared with the other NSAID groups and the no-NSAID group ($P = .032$ at 4 weeks and $P = .252$ at 8 weeks).

CONCLUSIONS: The topical NSAIDs ketorolac 0.4%, bromfenac 0.09%, and nepafenac 0.1% were effective for the reduction of postoperative inflammation following phacoemulsification. Compared with ketorolac tromethamine, bromfenac, and the control, nepafenac was significantly effective 1 month postoperatively in reducing anterior chamber flare, as evidenced by decreased laser flare photometry.

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One of the most common postoperative complications of phacoemulsification is anterior segment inflammation.[1] Intraocular inflammation causes disruption of the blood–ocular barriers and allows entry of proteins and inflammatory cells into the aqueous humor. If postoperative ocular inflammation remains uncontrolled over the long term, it can lead to various complications including cystoid macular edema (CME), corneal edema, anterior and posterior synechiae formation, and raised intraocular pressure (IOP).

Recent advances in cataract surgery have resulted in a decrease in the physical trauma associated with

such surgery and a subsequent decrease in the release and production of the chemical mediators that lead to postoperative ocular inflammation.[2] Despite recent improvements in cataract surgery and medications that have occurred during the past 5 years, most patients still exhibit clinically significant postoperative ocular inflammation after cataract surgery.

Anterior chamber inflammation can be graded by slitlamp examination or quantified by laser flare photometry. Slitlamp examination allows only a subjective and arbitrary grading of cells and flare (protein) in the anterior chamber. Slitlamp findings may have interobserver variation, and the experience of the observer plays a major role in the interpretation of the findings. Laser flare photometry is the only objective and quantitative method to reliably measure intraocular inflammation.[3] Laser flare photometry is also the only technique to measure intraocular inflammation in a noninvasive way. It can reliably measure the level of inflammation, and several studies have shown increased flare values after surgery in the postoperative period.[4–6] Flare level usually peaks on the first postoperative day and declines rapidly in the first week postoperatively after cataract surgery.[4]

Topical steroid therapy effectively treats inflammation but can increase IOP, inhibit wound healing, and increase the likelihood of an infection or worsen an existing one.[7,8] Several clinical studies have shown that nonsteroidal antiinflammatory drugs (NSAIDs) are as effective as steroids in the treatment of postoperative pain and inflammation.[9–12] A combination therapy of steroids with NSAIDs has been shown to produce a synergistic effect on postoperative inflammation.[13]

This study was carried out to evaluate the effect of topical ketorolac 0.4% (Acular LS), bromfenac 0.09% (Megabrom), and nepafenac 0.1% (Nevanac) on the inhibition of postoperative inflammation in terms of anterior chamber flare measured by laser flare photometry in patients having phacoemulsification with posterior chamber intraocular lens (PC IOL) implantation. To our knowledge, there is no prospective randomized study comparing the antiinflammatory effect of these commonly used topical NSAIDs following phacoemulsification using laser flare photometry.

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PATIENTS AND METHODS

Study Group and Protocol

This single-center prospective randomized study included patients with visually significant age-related cataract having phacoemulsification with PC IOL implantation. All surgeries were performed between July 2013 and June 2014. The study was approved by the institutional ethical committee, and all of the patients signed written informed consent forms before study enrollment.

Patients with visually significant age-related cataract who were 40 years or older of either sex having phacoemulsification with PC IOL implantation were enrolled. Exclusion criteria were prior ocular trauma or intraocular surgery; history of uveitis; eyes with corneal disease, pseudoexfoliation syndrome, or ocular infection; history of coexistent ocular disease such as glaucoma, optic atrophy, or ocular tumors; history of use of topical steroids, NSAIDs, or prostaglandins within 2 weeks of enrollment; eyes with complications from diabetic mellitus; uncontrolled hypertension; any connective tissue disorders, serious renal, hepatic, endocrine, pulmonary, cardiac, neurologic, rheumatic, psychiatric, or cerebral dysfunction; and ocular allergy to ketorolac, bromfenac, or nepafenac.

The patients were randomly divided into 1 of 4 groups using a computer-generated random-number table, as follows: Group A (ketorolac group), Group B (bromfenac group), Group C (nepafenac group), and Group D (control group [no NSAID]). Patients were instructed to instill a topical antibiotic (moxifloxacin 0.5%) 6 times a day and the NSAID 2 times a day (bromfenac 0.09%) or 3 times a day (ketorolac 0.4% and nepafenac 0.1%) 1 day before surgery. On the day of surgery, they were instructed to instill 1 drop of the NSAID 3 times at 30-minute intervals, along with the dilators tropicamide 0.8% plus phenylephrine 5.0% and cyclopentolate hydrochloride 1.0% in the morning. Local anesthesia was administered with topical proparacaine hydrochloride 0.5%, followed by a peribulbar injection using a mixture of bupivacaine 0.5% and lignocaine 2.0% mixed with adrenaline and hyaluronidase. The same surgeon (J.R.) performed all of the cataract surgeries using a standard clear corneal phacoemulsification technique. The same irrigation solution comprising a balanced salt solution (BSS, Alcon Laboratories, Inc.) and an ophthalmic viscosurgical device (sodium hyaluronate 1.4% [Healon GV]) were used in all cases. A hydrophobic acrylic IOL was implanted in the capsular bag in all cases.

Laser flare photometry was done using the FM-600 (Kowa Co. Ltd.). Measurements were obtained preferably at the same time of the day on scheduled visits. Readings were discarded if the 2 background measurements differed by more than 15%. A reading of "0," which indicates an inability to calculate a difference from background, was discarded. Seven laser flare photometry measurements with values greater than 0 and whose backgrounds differed by less than 15% were saved; the highest and lowest values were discarded, in accordance with the manufacturer's guidelines, and the remaining 5 measurements were averaged. Measurement conditions were kept constant for all patients. All patients had normal brown irises. All measurements (preoperative as well as postoperative) were taken with undilated pupils.

Table 1. Characteristics of study patients.

Characteristic	Ketorolac 0.4% (Group A) (n = 33)	Bromfenac 0.09% (Group B) (n = 30)	Nepafenac 0.1% (Group C) (n = 31)	No NSAID (Group D) (n = 26)
Male, n (%)	19 (57.6)	15 (50.0)	18 (58.1)	15 (57.7)
Female, n (%)	14 (26.4)	15 (50.0)	13 (41.9)	11 (42.3)
Age (y)				
Mean ± SD	63.48 ± 9.60	59.63 ± 8.96	60.42 ± 10.72	60.77 ± 9.65
Range	40, 80	41, 75	40, 80	40, 80

NSAID = nonsteroidal antiinflammatory drug

Each of the patients was given the topical NSAID according to the group to which they were randomized and also received the standard post–cataract surgery regimen that included an antimicrobial agent, a topical steroid agent, and artificial tears. The topical antibiotic (moxifloxacin 0.5%) and steroid (prednisolone acetate 1.0%) drops were administered in the same daily dosages and tapered postoperatively. The topical NSAID was started preoperatively and continued in the same dosages in the respective groups for 6 weeks. Patients in the control group did not receive a topical NSAID. The tapering regimen for the topical steroid was as follows: 4 times a day for 7 days, 3 times a day for 3 days, twice a day for 3 days, once every day for 3 days, and then discontinued. Postoperative follow-up was at 1 day and 1, 2, 4, and 8 weeks. The routine examination at each visit included the corrected distance visual acuity (CDVA) on the Snellen chart; IOP using Goldmann applanation tonometry, posterior segment examination, and laser flare photometry using the laser flare photometer.

Statistical Analysis

All calculations were performed using SPSS software (version 17, SPSS Inc.). Continuous data are presented as the mean ± SD or median and interquartile range. Normality of quantitative data were checked by measures of Kolmogorov-Smirnov tests of normality. Normally distributed continuous variables among 3 groups were analyzed by 1-way analysis of variance, followed by post hoc multiple comparisons. For skewed data, the Kruskal-Wallis test was applied for 3 groups. The Mann-Whitney *U* test was used for statistical analysis of skewed continuous variables for 2 groups. For skewed data, time-related variables were compared by the Wilcoxon signed-rank test. Qualitative or categorical variables were described as frequencies and proportions. Proportions were compared using the chi-square or Fisher exact test, whichever was applicable. All tests were 2 sided. For all calculations, the CDVA was converted into logMAR visual acuity. A *P* value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Table 1 lists the characteristics of the 120 patients (120 eyes). The mean patient age was 61.14 years ± 9.76 (SD). Of the patients, 67 were men (55.8%) and 53 were women (44.2%). Table 2 shows baseline clinical profiles, which were homogenous in all groups.

One-day postoperative laser flare photometry values were significantly higher than baseline preoperative laser flare photometry values in all 4 groups ($P < .001$); however, the laser flare photometry values were not significant at any other postoperative visit. The highest values were on the first postoperative day. The values declined rapidly in the first week and then more gradually to the baseline preoperative levels by 2 months postoperatively.

The laser flare photometry values at the end of 4 weeks were minimal in the nepafenac group and maximal in the control (no-NSAID) group, which was statistically significant. The laser flare photometry values at the end of 8 weeks were minimal in the nepafenac group and maximal in the bromfenac group. Table 3 shows the comparison of laser flare photometry values during the postoperative period among all 4 groups.

Table 2. Preoperative clinical parameters.

Variable	Mean ± SD				*P* Value
	Group A (Ketorolac 0.4%)	Group B (Bromfenac 0.09%)	Group C (Nepafenac 0.1%)	Group D (No NSAID)	
CDVA (logMAR)	0.80 ± 0.62	0.70 ± 0.58	0.85 ± 0.83	0.89 ± 0.53	.319
IOP (mm Hg)	15.61 ± 2.98	14.03 ± 2.76	14.71 ± 4.00	14.04 ± 2.16	.106
LFP (ph/ms)	10.24 ± 5.16	10.89 ± 5.68	8.94 ± 4.24	10.06 ± 5.82	.530

CDVA = corrected distance visual acuity; IOP = intraocular pressure; LFP = laser flare photometry

Table 3. Laser flare photometry value (ph/ms) comparison between groups over time.

Visit	Mean ± SD				*P* Value
	Group A (Ketorolac 0.4%)	Group B (Bromfenac 0.09%)	Group C (Nepafenac 0.1%)	Group D (Control)	
Preoperative	10.24 ± 5.16	10.89 ± 5.68	8.94 ± 4.24	10.06 ± 5.82	.530
Postoperative					
1 d	29.18 ± 22.98	37.92 ± 37.11	29.70 ± 19.26	32.02 ± 24.41	.560
1 wk	15.29 ± 7.39	16.18 ± 8.75	14.85 ± 10.58	16.15 ± 9.34	.925
2 wk	10.53 ± 5.00	12.58 ± 5.65	11.43 ± 7.39	13.22 ± 6.59	.350
4 wk	10.68 ± 5.02	11.1 ± 7.69	8.62 ± 3.82	13.55 ± 7.60	.032
8 wk	10.52 ± 6.58	12.05 ± 7.06	9.02 ± 3.58	11.15 ± 6.06	.252

Nepafenac was significantly more effective in reducing anterior chamber flare 1 month postoperatively, as evidenced by decreased laser flare photometry values compared with ketorolac tromethamine, bromfenac, or no NSAID (Figure 1).

There was statistically significant improvement in CDVA postoperatively in all 4 groups that was comparable among all 4 groups. The between-group differences in visual outcomes were not statistically significant. The mean visual acuity comparison (in logMAR) at various time intervals of patients is shown in Table 4. The IOP values were comparable in all groups before and after surgery at all visits.

None of the patients reported any adverse effects related to topical NSAID use. An adverse event was seen in 1 patient (nepafenac group) in the form of a posterior capsule tear during phacoemulsification, in which the 3-piece hydrophobic acrylic IOL was placed in the sulcus. The patient developed a rhegmatogenous retinal detachment at 4 weeks that was subsequently managed with a pars plana vitrectomy. An epiretinal membrane was detected at 4 weeks in another patient (nepafenac group). These 2 patients were also included in the study.

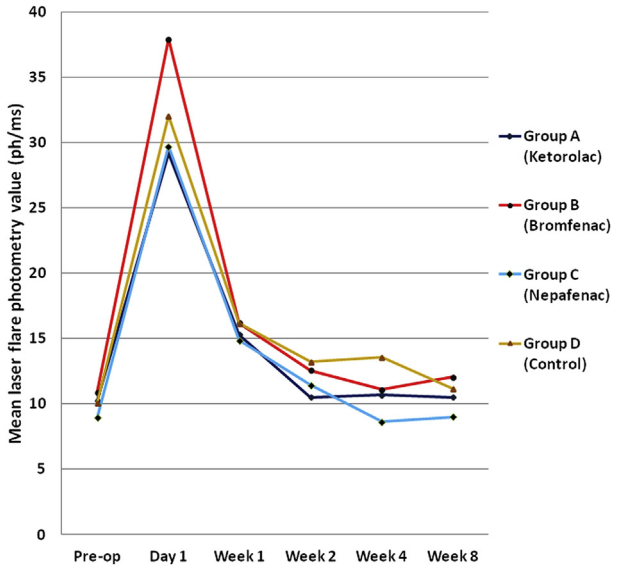

Figure 1. Mean laser flare photometry value (ph/ms) comparison over time.

DISCUSSION

Phacoemulsification with PC IOL implantation is the most common surgery performed worldwide. Some amount of intraocular inflammation is unavoidable, despite advances in surgical techniques and materials used.

In this prospective randomized study, we used laser flare photometry to analyze the ability of 3 commonly used topical NSAIDs to reduce flare in patients having phacoemulsification surgery. The postoperative anterior chamber inflammation was well controlled by all 3 topical NSAIDs. Overall, nepafenac 0.1% was associated with a decreased flare as measured by laser flare photometry compared with other topical NSAIDs and the control at 4 weeks. However, in this study, we acknowledge that during the postoperative laser flare photometry measurement, the IOL caused forward scattering of the light, providing the increased background light scatter that may have led to some data variability.

Bucci and Waterbury[14] compared the ability of topical NSAIDs to inhibit prostaglandin E_2 (PGE_2). In that study, 121 patients were randomized to 1 of 3 NSAID treatment arms (ketorolac 0.45%, bromfenac 0.09%, or nepafenac 0.1%). The aqueous humor (0.15 cc) was collected just prior to the surgery, and assays were conducted to measure the PGE_2 in cell culture supernatants. The study concluded that ketorolac 0.45% achieved the greatest inhibition of PGE_2 compared with nepafenac 0.1% and bromfenac 0.09% and suggested that ketorolac 0.45% may be more efficacious in controlling inflammation at the time of cataract surgery compared with nepafenac 0.1% and bromfenac 0.09%.

In another study, Bucci and Waterbury[15] compared the aqueous penetration of ketorolac 0.45%, bromfenac

Table 4. Mean logMAR CDVA at various postoperative visits.

Visit	Mean ± SD				*P* Value
	Group A (Ketorolac 0.4%)	Group B (Bromfenac 0.09%)	Group C (Nepafenac 0.1%)	Group D (Control)	
Preoperative	0.8 ± 0.62	0.7 ± 0.58	0.85 ± 0.83	0.89 ± 0.53	.32
Postoperative					
1 wk	0.22 ± 0.22	0.14 ± 0.12	0.14 ± 0.14	0.28 ± 0.30	.65
4 wk	0.1 ± 0.12	0.09 ± 0.10	0.07 ± 0.12	0.1 ± 0.12	.57
8 wk	0.1 ± 0.12	0.08 ± 0.10	0.08 ± 0.14	0.09 ± 0.12	.63

0.09%, and nepafenac 0.1% in cataract patients having phacoemulsification. In that study, 122 patients were randomized to 1 of 3 treatment arms. Aqueous humor (0.15 cc) was collected through the peripheral clear cornea just prior to the surgery, and drug concentrations were analyzed by liquid chromatography, tandem mass spectrometry, and multiple reaction monitoring mode for quantification. The study concluded that ketorolac 0.45% achieved significantly greater aqueous concentrations than bromfenac 0.09% and the active metabolite of nepafenac 0.1%.

Duong et al.[16] compared the clinical, subjective, and objective outcomes of the use of ketorolac tromethamine 0.4% and nepafenac 0.1% in patients having cataract surgery. Topical prednisolone 1.0% in addition to topical NSAIDs were used postoperatively in all cases for about 2 weeks in a tapering dosage. The investigators found that ketorolac tromethamine was statistically significantly better than nepafenac in terms of patient satisfaction, compliance, and postoperative pain control. However, the between-group differences in visual outcomes and anterior chamber inflammation evaluated using slitlamp biomicroscopy were not statistically significant (mean $P = .33$).

Tzelikis et al.,[17] in a prospective placebo-controlled randomized study, compared the antiinflammatory efficacy of ketorolac tromethamine 0.4% and nepafenac 0.1% eyedrops for prophylaxis of CME after small-incision cataract extraction. The incidence and severity of CME were evaluated by retinal foveal thickness on optical coherence tomography after 1, 4, and 12 weeks. All patients received topical prednisolone 1.0% in a tapering dose for 4 weeks, along with the topical NSAIDs. The authors concluded that when used prophylactically after uneventful cataract surgery, NSAIDs were not efficacious in preventing macular edema compared with placebo. Postoperative inflammation was not assessed in their study. Topical NSAIDs were shown to have antiinflammatory effects due to the inhibition of prostaglandin synthesis,[18,19] and combination therapy consisting of steroids with NSAIDs produced a synergistic effect on postoperative inflammation.[13]

A limitation of our study was the small sample. Also, other intraoperative factors that influence the amount of the flare postoperatively, such as energy used during the surgery (cumulative dissipated energy) or the duration of the surgery, were not calculated. In addition, it was not a masked or blinded study.

WHAT WAS KNOWN

- Topical NSAIDs have antiinflammatory effects due the inhibition of prostaglandin synthesis.
- Combination therapy of steroids with NSAIDs produces a synergistic effect on postoperative inflammation. Topically applied ophthalmic NSAIDs are used widely in the management of postoperative ocular inflammation.

WHAT THIS PAPER ADDS

- All 3 commonly used topical NSAIDs were effective in reducing postoperative inflammation after phacoemulsification. Compared with ketorolac tromethamine, bromfenac, or the control, nepafenac was significantly better for anterior chamber flare reduction, as evidenced by decreased laser flare photometry values at 4 weeks.

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