

# Relative effectiveness of topical ketorolac and topical diclofenac on discomfort after radial keratotomy

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## ABSTRACT

Two prospective, randomized, double-masked studies were conducted evaluating the analgesic effect of topical eyedrops after radial keratotomy (RK). One study of 117 consecutive initial RK procedures compared topical ketorolac (Acular®) with topical diclofenac (Voltaren®), and another study of 23 consecutive initial RK procedures compared topical ketorolac with a control medication (HypoTears®). Topical ketorolac was significantly more effective than the control but not significantly different from topical diclofenac. The onset of analgesic effect of these topical nonsteroidal anti-inflammatory drugs is longer than one hour. The analgesic effect of oral acetaminophen #3 significantly augments that of topical diclofenac drops for those experiencing any discomfort by six hours after surgery.

**Key Words:** acetaminophen #3, diclofenac, ketorolac, pain, radial keratotomy

Topical diclofenac sodium 0.1% (Voltaren®), a nonsteroidal anti-inflammatory drug (NSAID), has been shown to be effective in relieving ocular discomfort that can occur after both radial keratotomy (RK)<sup>1</sup> and excimer laser photorefractive keratectomy (PRK).<sup>2-4</sup> The drug reduces corneal sensitivity in healthy adult human volunteers not having surgery<sup>5</sup> and in rabbits.<sup>6</sup> Ketorolac tromethamine ophthalmic solution (Acular®), another NSAID, is now widely available. Arshinoff et al.<sup>7</sup> found that combinations of Acular or Voltaren ophthalmic solution with homatropine and soft contact lenses were effective in reducing post-PRK pain.

The present studies sought to determine whether topical ketorolac differed significantly from topical diclofenac and from a control (HypoTears®) in amount of relief offered from post-RK ocular discomfort.

## SUBJECTS AND METHODS

A prospective, randomized, double-masked study design was used with each of two separate series of consecutive RK procedures to compare topical ketorolac first with topical diclofenac and then with the

control. All patients in both series signed consent forms to participate. The surgeon (R.L.E.), office staff, and patients were masked from knowing which medication was used in each case.

The first series consisted of 117 eyes that had not previously had corneal surgery; 58 of these received diclofenac sodium 0.1% and 59, topical ketorolac tromethamine. The RK procedures were performed with the patient under topical anesthesia (proparacaine). As the last step of the procedure, one drop of tobramycin was applied to the operated eye. Topical diclofenac or ketorolac was applied approximately 30 seconds after surgery, and the unlabeled bottle was given to the patient with instructions to apply one drop to the operated eye four times daily for one week.

Patients also received a questionnaire to fill out at home. The questionnaire asked the postoperative discomfort level at 15 minutes, 1 hour, 3 hours, 6 hours, and 18 hours. A scale for discomfort was as follows: 0 for "none," 1 for "very slight," 2 for "slight," 3 for "mild," 4 for "moderate," 5 for "severe," and 6 for "the worst pain in my life." In addition, the questionnaire asked the number and type of postoperative

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Table 1. Discomfort level of patients treated with ketorolac versus diclofenac at time intervals after RK.

Postoperative Interval by Treatment Group*	Discomfort Level						Percentage with Pain < Mild	Statistical Analysis of Difference Between Treatment Groups			
	None	Barely	Slight	Mild	Moderate	Severe		Gamma	Asymptotic Standard Error	P-value	Significance at P = .05 Level (Two-Tailed Test)
15 minutes								-0.13	0.133	0.328	NS†
Ketorolac	18	13	15	7	3	3	78.0				
Diclofenac	17	23	8	6	4	0	82.8				
1 hour								-0.089	0.129	0.49	NS
Ketorolac	10	8	14	14	9	4	54.2				
Diclofenac	8	14	12	14	10	0	58.6				
3 hours								-0.133	0.129	0.303	NS
Ketorolac	11	4	16	15	11	2	52.5				
Diclofenac	13	9	13	11	12	0	60.3				
6 hours								-0.136	0.13	0.295	NS
Ketorolac	13	10	14	13	9	0	62.7				
Diclofenac	17	12	12	8	9	0	70.7				
18 hours								-0.199	0.135	0.14	NS
Ketorolac	19	12	14	13	1	0	76.3				
Diclofenac	15	13	11	7	2	0	84.5				

\* Ketorolac group N = 59; diclofenac group N = 58

† NS = not significant

Table 2. Discomfort level\* of patients treated with ketorolac and HypoTears at various postoperative intervals.

Postoperative Interval	Discomfort Level		Gamma	Asymptotic Standard Error	P-value	Significance at P = .05 Level (Two-Tailed Test)
	None to Mild	Moderate to Severe				
15 minutes			-0.109	0.284	0.70	NS†
Ketorolac	7	4				
HypoTears	8	4				
1 hour			0.423	0.247	.09	NS
Ketorolac	7	4				
HypoTears	6	6				
3 hours			0.874	0.103	.0001	S‡
Ketorolac	9	2				
HypoTears	3	9				
6 hours			0.984	0.022	.0001	S
Ketorolac	10	1				
HypoTears	5	7				
18 hours			0.737	0.170	.00001	S
Ketorolac	10	1				
HypoTears	9	3				

\* Discomfort level responses are summarized in two categories.

† NS = not significant

‡ S = significant

Table 3. Discomfort level of patients treated with diclofenac alone (Epstein and Laurence<sup>1</sup>) versus diclofenac with oral acetaminophen #3 (present study) at time intervals after RK.

Postoperative Interval	Gamma	Asymptotic Standard Error	P-value	Significance at P = .05 Level (One-Tailed Test)
15 minutes	-0.79	0.154	0.608	NS*
1 hour	0.054	0.156	0.739	NS
3 hours	0.161	0.155	0.299	NS
6 hours	0.306	0.152	0.044	S†
18 hours	0.359	0.148	0.015	S

\* Not significant. Adding acetaminophen to diclofenac does not provide significantly greater discomfort relief than diclofenac alone at this time interval post-RK.

† Significant. Adding acetaminophen #3 to diclofenac provides significantly greater discomfort relief than diclofenac alone at this time interval post-RK.

Table 4. Discomfort level of patients treated with Tears Naturale versus HypoTears at time intervals after RK.

Postoperative Interval	Gamma	Asymptotic Standard Error	P-value	Significance at P = .05 (One-Tailed Test)
15 minutes	0.430	0.210	0.044	S*
1 hour	0.423	0.209	0.043	S
3 hours	0.382	0.216	0.077	NS†
6 hours	0.384	0.205	0.061	NS
18 hours	0	0.252	1	NS

\* S = significant

† NS = not significant

analgesic, if any, used during the first 24 hours after surgery.

All patients received 8-incision, 12-incision, or 16-incision RK with an initially centrifugal incision. Some patients, identified by the surgeon's previously described computer software,<sup>1</sup> also received a centripetal incision at the 3.00 mm or 2.75 mm optical zone. All procedures were performed using one of a set of identical Genesis® (KMI Surgical Products, West Chester, PA) diamond RK knives. When needed, astigmatic arcuate keratotomy (AK) was performed just before the radial incisions and was modified with intraoperative videokeratographic guidance.

The number of eyes receiving 8-, 12-, and 16-incision RKs and the number of eyes receiving AK were approximately equally distributed among the subgroups. In the ketorolac group, the number of eyes receiving 8-, 12-, and 16-incision RKs were 45, 6, and 8, respectively. In the diclofenac group, the number of eyes were 51, 2, and 5, respectively. Astigmatic ker-

atotomy was performed on 26 of 58 ketorolac-treated eyes and on 27 of 59 diclofenac-treated eyes.

In the second series of 23 eyes, 11 had ketorolac and 12, the control (HypoTears). In both cases, the medication was applied 30 seconds after the end of the operation, and patients were instructed to reapply drops to the operated eye four times daily for one week. Unlike patients in the first series, these patients also received a prescription for 15 acetaminophen #3 with instructions to take one analgesic every four hours if needed for pain.

Statistical analyses were performed using the SAS program and employing nonparametric methods with asymptotic standard error theory. Pain level data at each of the postoperative times were analyzed using the Gamma statistic of Goodman and Kruskal.<sup>8,9</sup> Gamma is equal to  $(C - D)/(C + D)$ , where  $C$  is the sum of all concordant products and  $D$  is the sum of all discordant products for categorical ordinal data. The Gamma statistical test was applied to the data for each postoperative time period. The test is "asymptotically normally distributed" (i.e., normally distributed for larger sample sizes); therefore, test results can be approximately converted into  $P$ -values. The Gamma statistic can also be interpreted as a correlation coefficient for ordinal categorical data. The asymptotic standard error can be interpreted as the error in the estimate of the correlation coefficient, Gamma. Therefore, for statistical significance at the 5% level, the Gamma statistic must be away from zero by an amount at least 1.96 times the asymptotic standard error.

The effect of prescribing acetaminophen #3 as an adjunct to diclofenac was analyzed by combining the data of the current clinical trial with that of our previous one,<sup>1</sup> which used the identical surgical technique and study methodology. In the current trial, the control substance was HypoTears, whereas in the earlier study<sup>1</sup> it was Tears Naturale®. We compared the relative efficacy of Tears Naturale and HypoTears by combining data from the two studies.

## RESULTS

In the study comparing topical ketorolac with topical diclofenac, the difference between the two drugs was statistically insignificant ( $P = .05$ ) in each of the five time periods. Table 1 shows the number of responses in each discomfort category at each postoperative time for the diclofenac-ketorolac study. This table also lists the Gamma statistical value, the asymptotic standard error, and the calculated  $P$ -value for the null hypothesis that diclofenac and ketorolac do not differ significantly in effectiveness. Table 1 does suggest a slight superiority of diclofenac over ketorolac in limiting pain to less than mild that might reach statistical significance in a comparison involving larger numbers of cases.

The second study found that, in general, patients receiving topical ketorolac were more comfortable than those receiving the control. Table 2 compares discomfort levels at the different postoperative periods and shows the Gamma statistic and asymptotic standard error for each period. As Table 3 indicates, ketorolac's pain-relieving superiority to the control medication becomes apparent only at three hours post-surgery and afterward.

One patient in each of the NSAID groups had mild punctate keratopathy at two weeks, although medication had been prescribed for only one week. No patient in the small HypoTears group had such a response.

## DISCUSSION

Comparing results of the present study with those of our previous one<sup>1</sup> on postoperative RK patients, we found that the combination of oral acetaminophen #3 with topical diclofenac added significantly more discomfort relief to that achieved by using diclofenac alone. The enhanced effect of acetaminophen #3 was significant at 6 hours and 18 hours postoperatively (Table 3) and thus would be helpful for patients whose discomfort, even with NSAID use, lasts six hours or longer.

Comparing the results of the present study using HypoTears with those of the previous one using Tears Naturale, we found that Tears Naturale offered a greater degree of discomfort relief than HypoTears during the first hour, but that that superiority became insignificant as more postoperative hours passed (Table 4).

Based on the findings of our current and previous studies, we would recommend that an oral analgesic such as acetaminophen #3 be given before surgery once each four hours for eight hours and thereafter optionally. We would recommend the use of either topical diclofenac or topical ketorolac at the end of the

operation and four times daily on the operated eye for three days. A thickened version of artificial tear solution instilled into the operated eye 5 to 10 minutes after surgery may give further relief of any discomfort since the nonsteroidals were more effective after several hours than immediately.

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