

Preoperative Topical Diclofenac and Ketorolac in Prevention of Pain and Discomfort Following Photorefractive Keratectomy: A Randomized Double-Masked Placebo-Controlled Clinical Trial

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ABSTRACT

Objectives: To compare the efficacy of a single dose of topical diclofenac 0.1% and ketorolac 0.5%, with placebo and with each other in the prevention of post-PRK pain and discomfort.

Methods: In this randomized double-masked trial, adults undergoing bilateral PRK surgery were assigned to two arms. The first arm received a single dose diclofenac 0.1%, randomly in either the right, or left eye, and artificial tear (as the placebo) in the other eye. The second arm received ketorolac 0.5%, by the same pattern. The primary outcome of this study was ocular^[1] pain assessed by visual analogue scale (VAS), and^[2] discomfort including itching, foreign body sensation, tearing and photophobia which were questioned in 4 degrees.

Results: In the final analysis, 47 and 36 subjects remained in the diclofenac and ketorolac treated arms, respectively. In both arms, on the first and second post-operation days, VAS scores were significantly lower in the pretreated eye. Moreover, on the first post-operation day, the intensity of all ocular discomfort items was statistically lower in the pretreated eyes; whereas, on the second day, such a difference was only observed for foreign body sensation and itching in the diclofenac treated arm and for photophobia in ketorolac treated arm. Comparison of the two arms (diclofenac pretreated eyes vs. ketorolac pretreated eyes) on both first and second post-operation days showed no significant difference neither in the VAS scores nor the ocular discomfort items.

Conclusions: Either diclofenac or ketorolac instilled at a dose of one drop 30 minutes in advance of the operation would be equally beneficial in the short-term prevention of post-PRK pain and discomfort.

Keywords: Photorefractive keratectomy, diclofenac, ketorolac, pain, discomfort, prevention

INTRODUCTION

Photorefractive keratectomy (PRK) is a reputed method of excimer laser corneal refractive surgery, shown to be effective and safe in the correction of refractive errors.^[1] This method has a

shorter operation duration, no micro-keratome usage and no flap complications in comparison to laser in situ Keratomileusis. However, short term pain and discomfort, and delayed recovery are its disadvantages.^[2] Moderate to severe pain has been a significant complication of PRK, especially during the first postoperative 24 hours and sometimes requires treatment with oral analgesic drugs. This pain usually onsets at the first hour after the operation, increases over the ensuing 3 to 4 hours, and then gradually subsides during the corneal re-epithelialization over a few days. This is mostly due to the ablation of the corneal surface that leads to exposure of highly sensitive nerves and the consequent inflammation.^[3,4] During the past decade, a growing body of scientific research has been devoted to promoting pain relief following PRK. In this respect and in line with their further ophthalmologic applications, topical non-steroidal anti-inflammatory drugs (NSAIDs) have attracted extensive attention. Several studies pointed toward the potency of diclofenac and ketorolac in the alleviation of normal corneal sensitivity and pain after corneal abrasions. Correspondingly, the only approved NSAIDs for refractive surgery in the United States are diclofenac 0.1% and ketorolac 0.4% and 0.5%.^[5-9] In the ophthalmologic and non-ophthalmologic literature, there are descriptions for both preoperative and postoperative application of NSAIDs.^[10-14] In the field of refractive surgery, these medications are shown to decrease postoperative pain and photophobia. These data are generally derived from postoperative analgesic methods; though, few valid studies have focused on the preoperative use of NSAIDs for the prevention of post-PRK pain.^[5-9] The only trial that specifically addressed the efficacy of preoperative NSAIDs in relieving post-PRK pain was recently performed by Mohammadpour *et al.* This study indicated the efficacy of a single drop of topical diclofenac 0.1%, 2 hours before the operation.^[15] Nevertheless, according to our knowledge in the field of refractive surgery, there is no study concerning such a use of ketorolac and its differences with

diclofenac. Therefore, we designed this study to compare the efficacy and safety of a single dose of topical diclofenac 0.1% and ketorolac 0.5%, with placebo and with each other in the prevention of post-PRK pain and discomfort.

METHODS

Ethics, consent and the participation criteria

The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Isfahan University of Medical Sciences. Data collection was in conformity with country laws, and a signed informed consent was obtained from each patient before the procedure. Patients were eligible for participation, if they were otherwise healthy, literate and older than 19 years of age, scheduled to undergo bilateral myopic excimer laser PRK after a documented refraction stability of at least 1 year. Difference in refraction between two eyes had to be smaller or equal to 1 diopter and corneal thickness of both eyes greater or equal to 480 μm . The exclusion criteria of the study consisted of: keratoconus and corneal pathology, use of systemic or topical anti-inflammatory medications within 2 weeks before the surgery, history of allergic reaction to aspirin or other NSAIDs, bleeding disorders, liver disorders, glaucoma and/or ocular hypertension (>20 mm Hg), endocrine or collagen vascular diseases, diabetic retinopathies, addiction and dependency on analgesic drugs, pregnancy/lactation, and intraoperative complications. Moreover, cases were excluded from the final analysis if they replaced or dislocated their contact lenses, or had postoperative trauma to the eye.

Design and setting

In this single-site randomized double-masked, paired-eye comparison, placebo-controlled clinical trial 120 adults undergoing elective PRK surgery were consecutively recruited in Feiz eye hospital, Isfahan, Iran, between January and July 2010 and were assigned to two arms of drug regimen using a random-numbered table. The first arm received a single

dose of topically applied diclofenac 0.1%, randomly in either the right or left eye, and artificial tear (as the placebo) in the other eye. The second arm received topically applied Ketorolac 0.5%, with the same pattern. This protocol was carried-out by a trained coordinator on an out-patient basis and the randomization was processed and maintained by our pharmacy employees. The randomization keys could be revealed if a patient reported side effects attributable to NSAIDs. Uniformly, drops were instilled 30 minutes before surgery and all eyes were operated by the same surgeon (H.R.), in a single refractive surgery center. Neither the surgeon nor the participants were told which eye had received the real medication. Pain and discomfort assessments were implemented by the patients who recorded their reports on the first and second postoperative days. Nonetheless, the process of writing diaries was under the direct supervision of trained technicians, who were unaware of the study sequence. Patients who experienced intolerable pain were authorized to take Acetaminophen 500 mg/day and, given such situations, they were requested to report their self-administrations. No other eye drops or analgesic tablets were permitted during the post-PRK period.

Surgical method

Following a 5% povidone-iodine scrub of eyelid and skin, topical Tetracain 1% was instilled into each eye before surgery. After the primary preparations, the cornea was de-epithelized by a blunt spatula, after the application of diluted 20% alcohol. The Technolas 217-z excimer system (Bausch & Lomb) was employed for laser ablation. Mitomycin 0.02% was applied to the stromal bed for up to 40 seconds, and then the surface was dried with a sponge and irrigated with a balanced salt solution. Then, topical ciprofloxacin drop was applied and soft bandage contact lenses (Acuvue; Johnson & Johnson Vision Care, Jacksonville, Fla) were placed. Postoperatively, topical betamethasone 0.1% was administered every 3 hours and

topical ciprofloxacin every 6 hours. For the detection of any complications, precise follow up and evaluation were implemented at days 1, 2, and 6, and months 1, and 3 after the operation.

Assessments

The primary outcome of this study was subjectively reported ocular pain and discomfort. All patients were educated on how to evaluate and score their ocular symptoms, and how to complete their pain and discomfort questionnaires on the first and second postoperative days. All assessments were performed separately for each eye. To evaluate ocular pain, we used the Visual analogue scale (VAS), which is a scale graded from 0 to 10. "0" means no pain and "10" is the worst pain the patient has ever experienced. Ocular discomfort symptoms, including itching, foreign body sensation, tearing and photophobia were graded in 4 degrees: no symptom, mild, moderate and severe.

Statistical measures

Statistical data analyses were carried out by the SPSS version 20.0 and MedCalc version 10.2. Descriptive statistics were calculated for case characteristics. In order to compare age and spherical equivalent (SE) between the two study arms we used the independent sample *T*-test. Furthermore, for the comparison of sex and the number of patients who took oral pain medication on each postoperative day we applied appropriate χ^2 statistics. For within-group (contralateral eye) comparisons (diclofenac vs. placebo in the first arm and ketorolac vs. placebo in the second arm) regarding VAS and ocular discomfort scores, the wilcoxon test was applied. In order to compare the two arms (First arm: diclofenac vs. Second arm: ketorolac) regarding VAS and ocular discomfort scores the Mann-Whitney test was applied. For the comparison of the trend of VAS scores of the two arms, during two days of follow-up, repeated measures of analysis of variance were employed. Results have been expressed as a mean \pm SD (range), median (interquartile range [IQR]) or number (percent). All

tests were two sided and $P < 0.05$ was considered the significance threshold.

RESULTS

Of the initial 120 cases, 83 cases (20 male and 63 female) with mean age of 27.13 ± 6.00 years (Range: 19 to 53) completed the study and were eligible for the final analyses. The pre-PRK diagnosis in all enrolled patients was bilateral myopia, which was in some cases accompanied by astigmatism. Drop-out of the cases was due to (i) failure in referral to our center on the first, second or both post-operative days (4, 23, 5 cases, respectively), (ii) voluntary withdrawal from the study (2 cases), (iii) lost or replaced bandage contact lens (2 cases), or PRK related complications (1 case).

In the final analysis, 47 subjects (9 male, 38 female) with the mean age of 27.40 ± 5.44 and 36 subjects (11 male and 25 female) with the mean age of 26.77 ± 6.72 remained in diclofenac and ketorolac groups, respectively. No significant difference was caused by age ($P = 0.640$) and sex ($P = 0.288$) between the two groups. There was no difference between the mean pre-operative SE ($P = 0.151$) of eyes pretreated by diclofenac with those pretreated by ketorolac in the two study arms (4.36 ± 1.75 and 3.82 ± 1.58 , respectively). Proportion of acetaminophen self-administration was 12.8% (6/47) in the diclofenac treated arm and 8.3% (3/36) in the ketorolac

treated arm with no significant differences ($P = 0.725$). During the post-operative period, there were no complications attributable to administration of diclofenac or ketorolac, such as epithelial healing delays, corneal haze, and corneal melting or ulcer, either in cases included in the final analysis or in the excluded cases.

Data on within-group comparisons of pain and discomfort scores (contra-lateral eye studies) were as follows: in both arms, on the first and second postoperative days, VAS scores were significantly lower in the pretreated eye in comparison to the contralateral eye (Table-1). In both arms, on the first postoperative day, the intensity of all ocular discomfort items was statistically lower in the pretreated eyes. However, on the second day, such a difference was only observed for foreign body sensation and itching in the diclofenac treated arm and for photophobia in the ketorolac treated arm (Table 2).

Data on between group comparisons of pain and discomfort (diclofenac pretreated eyes vs. ketorolac pretreated eyes) were as follows: on both first and second postoperative days, no significant difference, neither regarding VAS scores nor ocular discomfort items, were observed (Tables 1 and 2). Moreover, during the follow up, no difference was observed between the trends of VAS scores of pretreated eyes pertaining to each study arm (Figure 1).

Table 1. Within and between group comparisons of scores of visual analogue scale during two postoperative days.

	VAS: day 1	VAS: day 2
Arm 1(n=47)		
Diclofenac	3 [0 to 5] (0-10)	6 [2 to 8] (0-10)
Placebo	7 [4 to 10] (0-10)	8 [6 to 10] (1-10)
*P	<0.0001	0.0001
Arm 2(n=36)		
Ketorolac	3 [0.25 to 6] (0-9)	6 [2.25 to 8] (0-10)
Placebo	7 [4 to 8] (0-10)	8 [6 to 9] (1-10)
*P	.0002	.0043
Arm 1 and 2		
**P	0.4499	0.6573

Note: Values of visual analogue scale (VAS) are presented as Median [median interquartile range] (Minimum, Maximum). *P was calculated by Wilcoxon test for within group comparisons (diclofenac vs. placebo and ketorolac vs. placebo). **P was calculated by Mann-Whitney for between group comparisons (diclofenac vs. ketorolac).

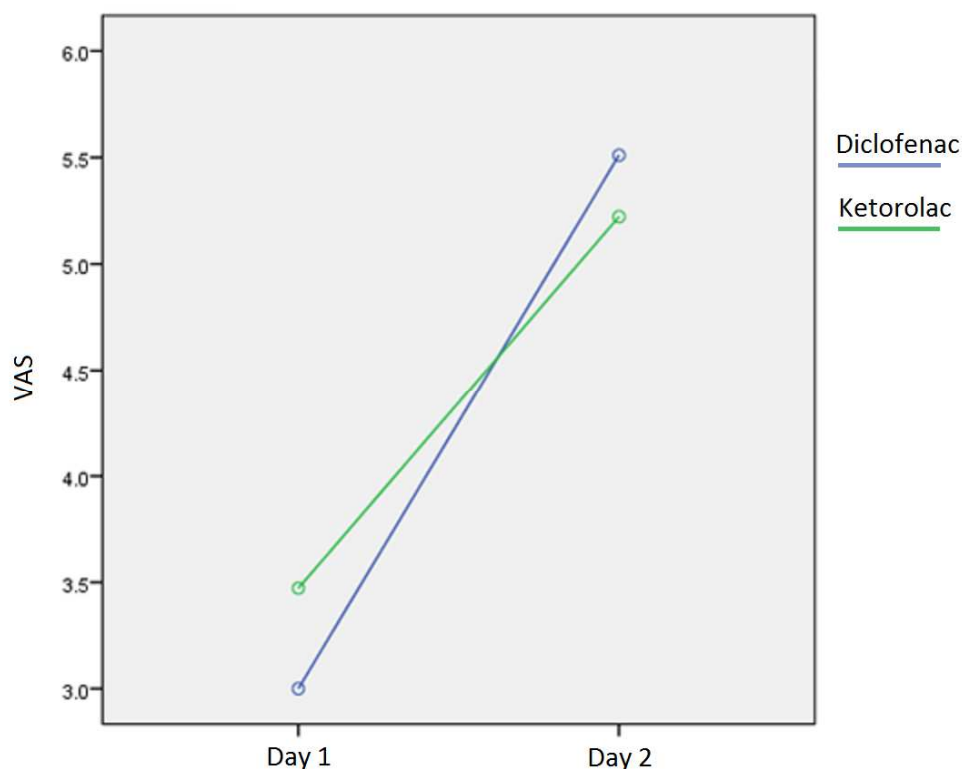


Figure 1. Intergroup comparison (pretreated eyes with diclofenac vs. those with ketorolac) of the trend of visual analogue scale (VAS) score during two post-op days (GLM Repeated Measures of ANOVA, $P = 0.875$).

Table 2. Within and between group comparisons of items of ocular discomfort during two postoperative days.

Item of ocular discomfort	Day 1				Day 2			
	Itching	F.B. sensation	Tearing	Photophobia	Itching	F.B. sensation	Tearing	Photophobia
Within group comparison: Arm 1 (n=47)								
Diclofenac	0.0 [0.0 to 1.0] (0.0-3.0)	1.0 [0.0 to 1.0] (0.0-3.0)	0.0 [0.0 to 1.0] (0.0-3.0)	2.0 [1.0 to 2.0] (0.0-3.0)	1.0 [0.0 to 2.0] (0.0-3.0)	1.0 [0.0 to 2.0] (0.0-3.0)	2.0 [0.0 to 2.75] (0.0-3.0)	2.0 [1.0 to 3.0] (0.0-3.0)
Placebo	1.0 [0.0 to 2.0] (0.0-3.0)	2.0 [1.25 to 3.0] (0.0-3.0)	2.0 [1.0 to 3.0] (0.0-3.0)	2.0 [2.0 to 3.0] (0.0-3.0)	1.0 [0.0 to 1.75] (0.0-3.0)	2.0 [1.0 to 3.0] (0.0-3.0)	2.0 [1.0 to 3.0] (0.0-3.0)	2.0 [1.0 to 3.0] (0.0-3.0)
*P	0.0012	< 0.0001	< 0.0001	0.0006	0.0446	0.0001	0.0739	0.0942
Within group comparison: Arm 2 (n=36)								
Ketorolac	0.0 [0.0 to 1.0] (0.0-2.0)	1.0 [0.0 to 2.0] (0.0-3.0)	1.0 [0.0 to 2.0] (0.0-3.0)	1.0 [1.0 to 2.0] (0.0-3.0)	1.0 [0.0 to 2.0] (0.0-3.0)	1.0 [1.0 to 2.5] (0.0-3.0)	2.0 [1.0 to 3.0] (0.0-3.0)	2.0 [1.0 to 3.0] (0.0-3.0)
Placebo	1.0 [0.0 to 1.0] (0.0-3.0)	2.0 [1.0 to 3.0] (0.0-3.0)	2.0 [1.0 to 3.0] (0.0-3.0)	2.0 [1.0 to 3.0] (0.0-3.0)	1.0 [0.0 to 1.5] (0.0-3.0)	2.0 [1.0 to 2.5] (0.0-3.0)	2.0 [1.0 to 3.0] (0.0-3.0)	2.5 [1.0 to 3.0] (0.0-3.0)
*P	0.0095	0.0450	< 0.0001	0.0076	0.6377	0.0934	0.8552	0.0273
Between groups comparison: Arm 1 and 2								
**P	0.357	0.233	0.231	0.927	0.744	0.526	0.540	0.637

Note: F.B.: Foreign body. Items are presented as Median [median interquartile range] (Minimum, Maximum). *P was calculated by Wilcoxon test for intragroup comparisons (diclofenac vs. Placebo and ketorolac vs. placebo). **P was calculated by Mann-Whitney for intergroup comparisons (diclofenac vs. ketorolac).

DISCUSSION

To our knowledge, this prospective, randomized, placebo-controlled, double-masked trial was the first of its kind in assessing the efficacy of a single dose of topical diclofenac 0.1% vs. placebo, topical ketorolac 0.5% vs. placebo, and their differences in prevention of post-PRK pain and discomfort. The administration of these two medications resulted in statistically significant reductions of VAS scores among pretreated eyes compared to those with placebo on the first and second postoperative days. This difference was clinically remarkable on the first postoperative day; whereas, on the second day, we believe that such a difference, though statistically significant, did not indicate a major clinical significance. Regarding ocular discomfort items, on the first postoperative day, both pretreatments resulted in statistically and clinically significant differences; however, on the second day differences were only observed for itching and foreign body sensation among the pretreated eyes in the diclofenac treated arm and for photophobia in the ketorolac treated arm. In a recent study that assessed the preemptive analgesic effect of topical diclofenac 0.1% when applied 2 hours before PRK and continued every 6 hours for two days, such an efficacy was only shown for the first postoperative day.^[15] Comparing the efficacy of diclofenac and ketorolac in pain and discomfort prevention, both medications were equally beneficial and the present study did not observe a benefit of neither of these drugs over each other. Overall, the whole body of these results mostly point toward the possibility of a short term prevention of post-PRK pain by these ophthalmic solutions of NSAIDs.

Post-PRK pain is mediated by prostaglandins synthesized by cyclooxygenase (COX). In the field of excimer laser corneal refractive surgery, it has been postulated that both quick and prolonged production of prostaglandin E₂ causes post-PRK pain and discomfort.^[5-7] NSAIDs as a class of analgesic agents can prohibit COX activ-

ities and prevent free-nerve stimulation and inflammation.^[5] Theoretically, these medications work best when they are administered prior to the beginning of inflammation.^[5,10-12] Ophthalmic solutions of diclofenac and ketorolac, similar to other NSAIDs prevent the release of prostaglandins by the inhibition of COX.^[6, 10] It is suggested that COX inhibitors prevent the synthesis of prostaglandins, while they have minor efficacy in antagonizing previously produced prostaglandins.^[16] Therefore, it can be proposed that short-term alleviation of post-operative pain and inflammation may be optimized using preemptive approaches in the administration of NSAIDs.^[10- 12, 15, 16] In the surgery literature, in terms of non-ophthalmologic operations, there are descriptions of using preemptive analgesia with NSAIDs to reduce the quantity of postoperative analgesic medications.^[10-12] In the ophthalmology literature, some reports concerning cataract surgery have established the anti-inflammatory effects of preemptive NSAIDs.^[5,16,17] Along with the efficacy of post-PRK usage of diclofenac and ketorolac, there are some reports of adverse effects with this fashion of administration e.g. delayed wound healing, more susceptibility to corneal ulcer, sub-epithelial opacity and corneal melting. These complications were generally noted post-operatively, when NSAIDs were taken for several days.^[18-20] In our study, preemptive administration of these agents in a single dose formed a safe protocol with less concern about adverse effects, and, as could be expected, we did not observe any side effects attributable to NSAIDs. Inherent to the prospective, randomized, double-masked design of the study, the main strength of our work was the assessment of the pure preventive effect of topically applied NSAIDs in a single dose without any further post-operative administrations. The limitation of this work was the high rate of drop out subjects of the initial cases during our follow-up. This was mainly due to the distance of our center from patients' homes.

In conclusion, ophthalmic solution of NSAIDs, either diclofenac or ketorolac instilled at a dose of one drop 30 minutes preoperatively would play an important role with the same efficacy in the short term prevention of post-PRK pain and discomfort. More studies with larger sample sizes are warranted to confirm these results.

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