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ORIGINAL RESEARCH

Survey of Postoperative Pain in Photorefractive Keratectomy Using Topical versus Oral Nonsteroidal Anti-Inflammatory Drugs

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Madeline Ripa[1]
Brent Betts[1]
Shagun Dhaliwal[1]
Kaidi Wang[1]
Severin Pouly[1]
Danli Chen[2]
Mark Mifflin[1]

[1]Department of Ophthalmology and Visual Sciences, John A. Moran Eye Center, University of Utah, Salt Lake City, UT, USA; [2]Division of Epidemiology, University of Utah, Salt Lake City, UT, USA

Purpose: To evaluate and compare postoperative pain following photorefractive keratectomy (PRK) in patients using a preventive regimen of oral versus topical nonsteroidal anti-inflammatory drugs (NSAIDs).

Patients and Methods: A prospective, randomized, longitudinal survey of postoperative PRK pain was performed on 157 subjects in a tertiary academic medical center setting. Patients were randomized to either topical ketorolac 0.4% every 12 hours or oral naproxen sodium 220 mg every 12 hours for 72 hours following PRK, beginning at the time of surgery. The primary outcome measure was the daily peak pain score from the validated numerical rating scale (NRS) for five days after surgery.

Results: The peak pain scores were significantly higher in the oral NSAID group (mean 5.82, SD 1.94) compared to the topical NSAID group (mean 4.2, SD 2.19) ($p<0.0001$) after PRK. When comparing each postoperative day after PRK, the pain scores from 24 to 48 hours (day 2) were significantly higher in the oral NSAID group (mean 5.17, SD 2.25) as compared to the topical NSAID group (mean 3.21, SD 2.09) ($p<0.0001$). Pain scores 24–72 hours after surgery (days 2 and 3) were higher than pain scores on days 1, 4, and 5 for both groups.

Conclusion: Twice daily oral naproxen sodium 220 mg is inferior to twice daily topical ketorolac 0.4% in the treatment of early postoperative pain after PRK. This study also identified a consistent trend in which pain scores were highest 24–72 hours after the procedure. This additional observation may be useful in understanding, preventing, and treating post-PRK pain.

Keywords: pain, refractive surgery, photorefractive keratectomy, nonsteroidal anti-inflammatory drugs, naproxen, ketorolac

Plain Language Summary

This study was performed to compare pain levels in patients using different pain control regimens after photorefractive keratectomy (PRK), a laser vision correction procedure. Half of the patients were treated with oral pain medication for three days and half the patients were treated with eye drops for three days from the same category of pain medication, called nonsteroidal anti-inflammatory drugs (NSAIDs). The patients completed a survey of their pain scores for the first five days after the procedure. Pain scores after PRK were lower with eye drops than oral NSAIDs. Pain scores were highest on the second and third days after the PRK for both medications.

Introduction

Photorefractive keratectomy (PRK) is a common vision correction surgery. The procedure involves removing the corneal epithelium before excimer laser treatment.

Correspondence: Mark Mifflin
Email mark.mifflin@hsc.utah.edu

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PRK yields visual outcomes similar to laser-assisted in situ keratomileusis (LASIK) while eliminating flap-related complications associated with LASIK.[1,2] PRK is also less likely to structurally destabilize the cornea, with a lower ectasia risk as compared to LASIK.[3] This may allow for safer laser vision correction in a broader range of patients including some with thinner corneas or mild topographic abnormalities.[4]

One common side effect of PRK is acute postoperative pain due to the removal of corneal epithelium during the procedure.[5] Bandage contact lenses have been shown to speed epithelialization and reduce postoperative pain after PRK.[6] Medications are also commonly used in an attempt to help alleviate postoperative pain. Eye drops including lubricants, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and cycloplegics may be used and oral analgesics are frequently recommended or prescribed.[7] Topical NSAIDs have been studied extensively for pain control following PRK, but may be associated with side effects including burning, stinging, conjunctival hyperemia, punctate keratitis, and delayed epithelial healing.[8–12] Oral NSAIDs are used for analgesia in many fields of medicine and offer a potential alternative to the use of topical NSAIDs for post-PRK pain control. Although oral NSAIDs avoid the ophthalmic side effects associated with topical preparations, overuse may result in gastrointestinal, renal, or hepatic problems.[13,14] The purpose of our study was to determine whether pain after PRK differs between patients using topical NSAIDs and oral NSAIDs preventively in the early postoperative period.

Materials and Methods

Study Design

A prospective, randomized patient survey involving 157 patients undergoing PRK was carried out at the John A. Moran Eye Center at the University of Utah between January 2017 and June 2019. The tenets of the Declaration of Helsinki were followed, and institutional review board approval was obtained from the University of Utah. Subjects were recruited after undergoing standard refractive surgery screening, and informed consent was documented after explanation of the nature and possible consequences of the study. Exclusion criteria included a history of prior refractive surgery, keratoconus, forme fruste keratoconus, significant asymmetry on corneal mapping, predicted residual stromal bed less than 320 microns, concurrent therapy with any systemic or topical NSAID, prescription eye drops within the 24 hours prior to the procedure, significant ocular surface disease, history of ocular herpetic disease, or any ocular pathology except refractive error. Patients with a history of poorly controlled diabetes or immunologic disease were also excluded.

Patients were anesthetized with two drops each of topical proparacaine hydrochloride 0.5% (Alcon Laboratories, Inc., Fort Worth, TX) and preservative free tetracaine hydrochloride 0.5% (Alcon) given 10 minutes prior to the procedure and then 5 minutes prior to the procedure, followed by a preparation with 5% povidone-iodine solution. The central 8.5 millimeters of corneal epithelium was scored with a marker and then exposed to 20% ethanol in balanced salt solution (BSS®, Alcon) placed in an 8 mm well for 35–40 seconds, followed by removal from the well with a surgical sponge, and then immediate rinsing with 3 mL of BSS. The residual BSS was dried with sponges, followed by epithelial removal. Laser ablation was performed using the Allegretto Wavelight EX500® (Alcon) excimer laser according to a surgeon-optimized nomogram. Mitomycin C 0.02% (MMC) was applied to the residual stromal bed for 12–20 seconds in eyes with a greater than 60-micron ablation depth. After ablation, the ocular surface was rinsed with chilled (2.8–4° C) BSS for 10 seconds, followed by 1–2 drops each of ketorolac tromethamine 0.4% (Acular LS®, Allergan Inc., Irvine, CA), gatifloxacin 0.5% (Pacific Pharma, Inc., Rancho Cucamonga, CA), prednisolone acetate 1% (Pred Forte®, Allergan Inc.), and bandage contact lens (Acuvue Oasys®, Johnson and Johnson Vision Care, Inc., Jacksonville, FL) placement, according to our previously described technique.[15] All patients underwent surgery in the early morning. For purposes of study analysis, the first 24 hours after surgery was considered "day 1," 24–48 hours post-op "day 2," and so on.

Patients were assigned to one of two treatment groups using a computer-generated simple randomization table. Group 1 received ketorolac 0.4% in both eyes every 12 hours and group 2 received oral naproxen sodium 220 mg every 12 hours for 72 hours following PRK. Study participants in both groups used topical gatifloxacin 0.5% and prednisolone acetate 1% 4 times daily for 7 days, with bandage contact lens removal on day 7. Oral hydrocodone-acetaminophen 5–325 mg was used every 4 hours as needed for breakthrough pain. Patients in both groups were instructed by the refractive study coordinator to rate the highest or peak pain level in either eye on at the end of each day on days 1–5. The patients recorded their pain using

a validated numerical rating scale (NRS) where the patients subjectively rated their pain on an eleven-point numerical scale, from 0 (no pain) to 10 (worst imaginable pain).[16]

Analysis

T-tests were used to compare the differences in mean peak pain scores and Chi-square tests were used to compare the differences in proportions between the two groups for sex, opioid, and MMC use. Fisher's exact test was used to compare peak pain on days 1 through 5 for the two study groups. Repeated measures mixed-effects models were used to test for differences in the means of the pain score for days 1 through 5 after controlling for opioid use and MMC. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance was assessed at the 0.05 level and all tests were two-tailed.

Results

One-hundred and fifty-seven patients participated in our study, with 78 patients enrolled in the topical ketorolac group and 79 patients in the oral NSAID group. Twenty-two patients had either no data or incomplete data for postoperative pain and were not included in pain score analysis. The mean age was 33.9 years with 71 men and 86 women. There was no significant difference in age or sex between the two groups (Table 1). The peak pain score after PRK was higher ($p<0.0001$) in the oral NSAID group (mean 5.82, SD 1.94) compared to the topical NSAID

Table 1 Summary Table

		All	Ketorolac	Oral NSAID	p value
Patients		135	68	67	
Day peak pain experienced[a]	Day 1	16(11.85%)	13(19.12%)	3(4.48%)	0.0051
	Day 2	69(51.11%)	26(38.24%)	43(64.18%)	
	Day 3	46(34.07%)	26(38.24%)	20(29.85%)	
	Day 4	3(2.22%)	2(2.94%)	1(1.49%)	
	Day 5	1(0.74%)	1(1.47%)	0(0.00%)	
Mitomycin C use	Total	157	78	79	0.7041
	No	129(82.17%)	65(83.33%)	64(81.01%)	
	Yes	28(17.83%)	13(16.67%)	15(18.99%)	
Hydrocodone-acetaminophen use	Total	157	78	79	0.5514
	Missing	74(47.13%)	35(44.87%)	39(49.37%)	
	No	58(36.94%)	32(41.03%)	26(32.91%)	
	Yes	25(15.92%)	11(14.10%)	14(17.72%)	
Sex	Total	157	78	79	0.1705
	Male	71(45.22%)	31(39.74%)	40(50.63%)	
	Female	86(54.78%)	47(60.26%)	39(49.37%)	
Average day of peak pain	Mean(SD)	2.29 (0.73)	2.29 (0.86)	2.28 (0.57)	0.9335
	Median(IQR)	2 (2–3)	2 (2–3)	2 (2–3)	
	Range	1–5	1–5	1–4	
Age	Mean(SD)	33.87 (6.16)	34.33 (5.91)	33.41 (6.39)	0.3465
	Median(IQR)	34 (29–38)	34 (31–38)	33 (28–39)	
	Range	21–49	21–49	21–49	
Average score[b]	Mean(SD)	2.39 (1.31)	2.19 (1.3)	2.6 (1.31)	0.0760
	Median(IQR)	2.2 (1.4–3.	1.9 (1.4–3)	2.4 (1.8–3.	
	Range	0.2–6.4	0.2–6.4	0.4–6.2	
Maximum score	Mean(SD)	5 (2.22)	4.2 (2.19)	5.82 (1.94)	<0.0001
	Median(IQR)	5 (3–7)	4 (3–6)	6 (4–7)	
	Range	0–10	0–10	1–10	

Notes: [a]The first 24 hours after surgery was considered "day 1," 24-48 hours post-op "day 2," and so on. [b]Pain scores rated using validated numerical rating scale.[16]
Abbreviation: NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; IQR, Interquartile range.

group (mean 4.2, SD 2.19). In addition, the pain score on day 2 was higher (p<0.0001) in the oral NSAID group (mean 5.17, SD 2.25) compared to the topical NSAID group (mean 3.21, SD 2.09) (Table 2). Pain scores in both groups were highest on days 2 and 3, with 51.11% of all patients reporting the peak pain score to occur between 24 and 48 hours after the procedure and 34.07% reporting peak pain between 48 and 72 hours (Table 1).

The use of MMC did not seem to correlate with pain scores, nor was the use of oral hydrocodone-acetaminophen 5–325 mg significantly different between the two groups (Table 1). When controlling for the differences in oral hydrocodone-acetaminophen use and MMC, peak pain remains highest in oral NSAID group (Tables 3 and 4). For each treatment, each individual patient's pain scores were graphed daily (Figures 1 and 2).

There were no complications in either group. All patients had complete epithelial healing by day 7 except for two eyes in the topical NSAID group. Four eyes in each group developed non-visually significant corneal haze by 6 months. Two eyes from each group required enhancement surgery. Ninety-one patients were followed for 6 months or longer while only 3 were lost to follow-up after less than 1 month. At last postoperative visit, 257 eyes were 20/20 or better, and 269 were 20/30 or better.

Discussion

Despite the safety and efficacy of PRK as a method of refractive surgery, postoperative pain remains a significant and potentially limiting side effect. The cornea is one of the most densely innervated tissues in the body.[17] Postoperative PRK pain is thought to occur due to the release of inflammatory mediators following the removal of the epithelial layer, which causes increased sensory nerve excitability.[18] While the magnitude of refractive error and ablation depth has not been found to correlate with pain levels, subjective preoperative dry eye symptoms are associated with higher postoperative pain scores.[5,19] The acute pain phase may begin shortly after the procedure and continues until re-epithelization at approximately day five.[7,20] Our findings suggest a consistent and identifiable trend in the postoperative pain course. Both groups experienced the highest levels of pain on days two and three (24–72 hours post-procedure), which then decreased through day five. The average peak pain level was noted to be 4.18 and 3.9 on days two and three respectively. This finding is consistent with previous studies, which found that pain peaks approximately 24–36 hours after the procedure.[5,20-23] Our data, however, demonstrate that peak pain levels often persist for up to 72 hours (day 3). These findings provide additional information about peak pain levels and timing

Table 2 Pain Score[a] for Postoperative Days 1 Through 5

Day[b]		All	Ketorolac	Oral NSAID	p value
Day 1	Mean(SD) Median(IQR) Range	2.04 (1.76) 2 (1–3) 0–10	2.02 (1.68) 2 (1–3) 0–10	2.07 (1.85) 2 (1–3) 0–8	0.8822
Day 2	Mean(SD) Median(IQR) Range	4.18 (2.38) 4 (2–6) 0–10	3.21 (2.09) 3 (2–4.5) 0–8	5.17 (2.25) 5 (3–7) 1–10	<0.0001
Day 3	Mean(SD) Median(IQR) Range	3.9 (2.2) 4 (2–5.5) 0–9	3.58 (2.01) 3 (2–5) 0–9	4.22 (2.34) 5 (2–6) 0–9	0.0945
Day 4	Mean(SD) Median(IQR) Range	1.25 (1.46) 1 (0–2) 0–7	1.38 (1.56) 1 (0–2) 0–7	1.11 (1.35) 1 (0–2) 0–5	0.2826
Day 5	Mean(SD) Median(IQR) Range	0.54 (1.15) 0 (0–1) 0–9	0.66 (1.39) 0 (0–1) 0–9	0.41 (0.83) 0 (0–0.5) 0–3	0.2044

Notes: [a]Pain scores rated using validated numerical rating scale. [b]The first 24 hours after surgery was considered "day 1," 24–48 hours post-op "day 2," and so on.[16]
Abbreviation: NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; IQR, interquartile range.

Table 3 Differences of Adjusted Means for Pain Score on the Same Day Between the Two Groups, Controlled for Hydrocodone-Acetaminophen 5–325 mg Use

Day	Ketorolac Group Adjusted Mean (95% CI)	Oral NSAID Group Adjusted Mean (95% CI)	Difference Between the Two Groups (95% CI)	p value
1	1.981 (1.528, 2.433)	2.039 (1.594, 2.484)	−0.059 (−0.667, 0.55)	0.8493
2	3.331 (2.782, 3.88)	5.224 (4.684, 5.764)	−1.893 (−2.631, −1.154)	<0.0001
3	3.732 (3.178, 4.285)	4.326 (3.784, 4.869)	−0.595 (−1.338, 0.149)	0.1158
4	1.417 (1.044, 1.79)	1.142 (0.775, 1.509)	0.275 (−0.227, 0.776)	0.2803
5	0.717 (0.424, 1.009)	0.46 (0.173, 0.748)	0.257 (−0.137, 0.65)	0.1989

Abbreviation: CI, confidence interval.

Table 4 Differences of Adjusted Means for Pain Score on the Same Day Between the Two Groups, Controlled for Hydrocodone-Acetaminophen 5–325 mg Use and MMC

Day	Ketorolac Group Adjusted Mean (95% CI)	Oral NSAID Group Adjusted Mean (95% CI)	Difference Between the Two groups (95% CI)	p value
1	1.973 (1.435, 2.511)	2.031 (1.49, 2.573)	−0.058 (−0.669, 0.553)	0.8511
2	3.586 (2.938, 4.234)	5.495 (4.842, 6.148)	−1.909 (−2.645, −1.173)	<0.0001
3	3.906 (3.251, 4.56)	4.512 (3.853, 5.17)	−0.606 (−1.35, 0.138)	0.1095
4	1.595 (1.155, 2.035)	1.332 (0.889, 1.775)	0.264 (−0.236, 0.763)	0.2985
5	0.979 (0.642, 1.317)	0.739 (0.4, 1.079)	0.24 (−0.143, 0.623)	0.2173

Abbreviation: CI, confidence interval.

after PRK, which may be valuable in counseling prospective patients as well as the care team.

Many strategies have been described to help minimize pain after PRK including bandage contact lenses, cold BSS, postoperative cold patches, NSAIDs, topical anesthetics, and opioids.[6–12,15,21,23,24] Even so, no established standardized approach to postoperative pain management exists. One study found a combination of topical anesthetic (amethocaine/tetracaine), topical diclofenac, and a bandage contact lens provided optimal postoperative pain management.[21] Other authors suggest that preoperative topical NSAIDs and a bandage contact lens or a bandage silicone hydrogel contact lens soaked in preservative free ketorolac 0.45% provide sufficient postoperative pain management.[22,25,26] A third report described the use of oral coproxamol in conjunction with topical tetracaine to be most effective.[20]

Short-term topical NSAIDs are frequently prescribed for post-PRK pain and are FDA-approved for this indication in the case of 0.1% diclofenac, 0.4% ketorolac, and 0.5% ketorolac.[8] Many different regimens of topical NSAIDs have been studied following PRK with equivalent efficacy regarding the reduction of pain and superiority compared to placebo.[7,8,10,11,22] Despite their benefits, postoperative topical NSAIDs may cause adverse effects including irritation, punctate keratitis, delayed epithelial healing, and corneal melt.[12,27] Multiple studies have shown delayed epithelialization of the cornea. A study with 200 patients found a 12-hour epithelial closure delay in patients taking ketorolac 0.5% every 4 hours for three days compared to controls.[10] Solomon et al. reported similar delayed corneal epithelialization (3.3 vs 2.7 days) in patients who received topical ketorolac 0.4% four times daily versus controls.[11] While these reported results are statistically significant, their clinical significance remains unclear. In addition to the above studies describing delayed epithelialization, Flach reported corneal melts in a case series of 11 patients following the use of topical diclofenac. However, they concluded that the inconsistent dose-toxicity relationships suggest that coexistent factors are implicated.[28] Gabison et al. also described a case of corneal perforation in a patient using topical diclofenac for two months following PRK.[29] Known co-morbidities for keratolysis or corneal melt include a history of ocular herpetic disease, severe dry eye, or uncontrolled autoimmune disease. Typically, topical NSAIDs are only utilized for three days following PRK and this short-term use in carefully screened surgery patients is recommended to minimize the chance for these adverse effects.

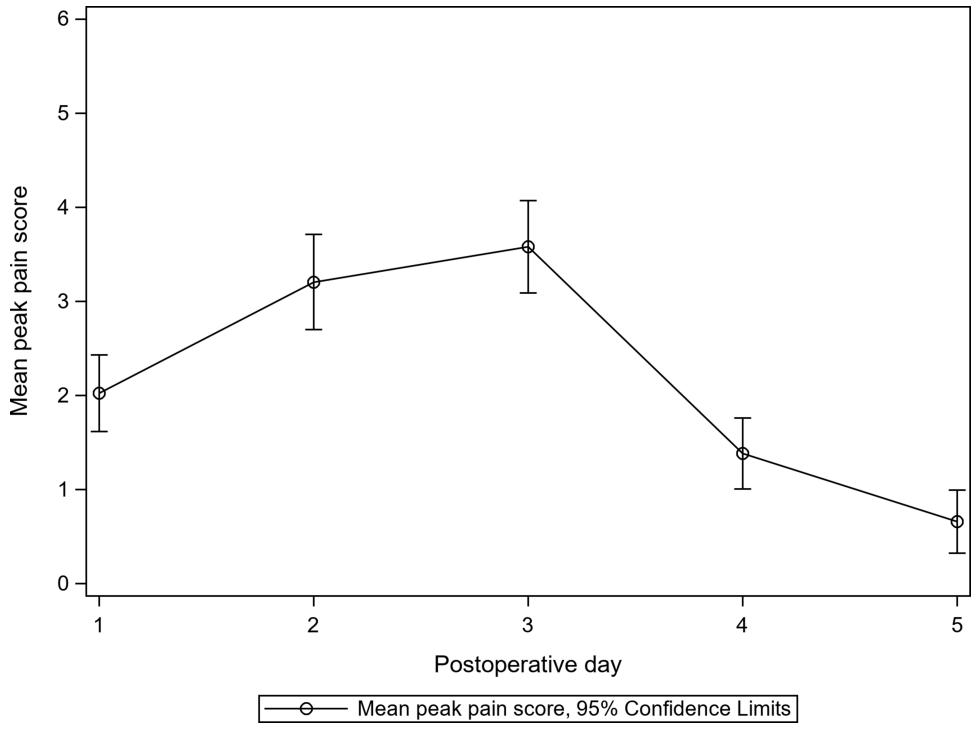

Figure 1 Average pain score for each patient in ketorolac group for postoperative days 1 through 5 after PRK.

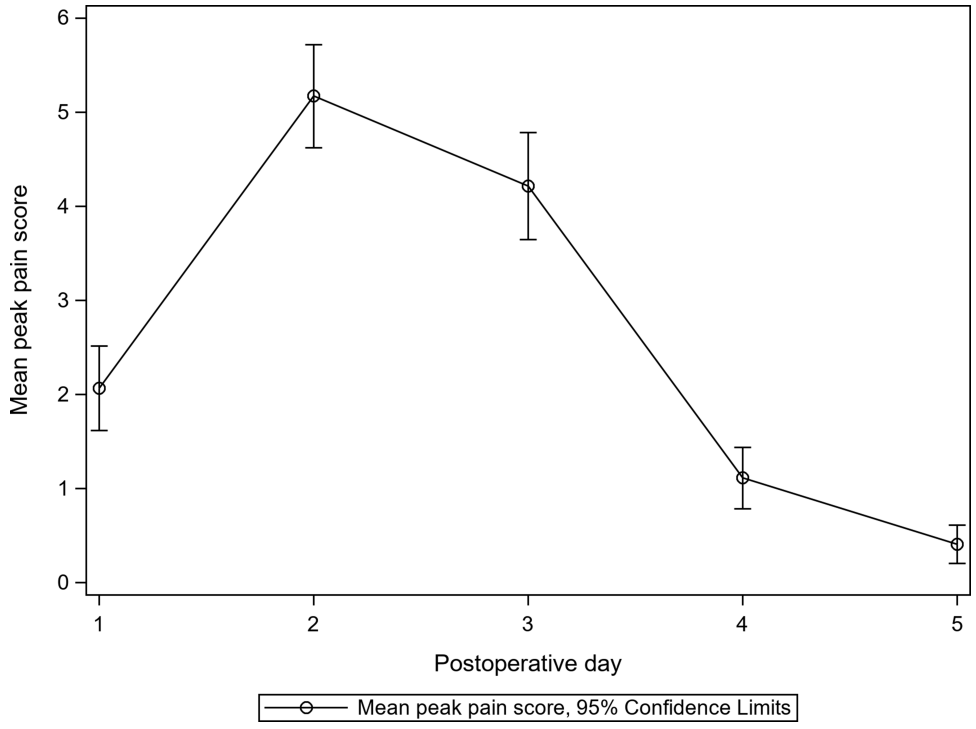

Figure 2 Average pain score for each patient in naproxen group for postoperative day 1 through 5 after PRK.

Our study is the first prospective study comparing oral naproxen to topical ketorolac for pain control after PRK. Oral NSAIDs are inexpensive, widely available, and avoid the local side effects to the ocular surface. Even so, sometimes serious gastrointestinal, renal, and hepatic side effects may occur.[13,14] Oral NSAIDs may also increase the risk of a medication interaction and are often contraindicated in patients with renal insufficiency.

Adverse effects are mainly prevalent with higher doses and prolonged use.[13,14]

When compared to oral NSAIDs, topical NSAIDs are more expensive for the patient and the healthcare system. For example, at our institution, topical 0.4% ketorolac costs approximately 40 US dollars compared to the approximately seven-dollar cost of over-the-counter naproxen. However, topical NSAIDs are only required for the first three days following PRK and do not result in a reoccurring financial cost.

Our findings show that oral naproxen, at a dose of 220 mg every 12 hours for three days, is inferior for postoperative PRK pain control compared to topical ketorolac 0.4% every 12 hours for three days. The most significant difference occurred on the second day after PRK and in the maximum pain scores between the two groups. After day 3, the pain scores were not significantly different between the two groups. There was no difference in the proportion of patients who used oral opiates for breakthrough pain. Given the potential adverse effects introduced by oral NSAIDs in addition to the overall lower pain scores with topical NSAIDs, this study suggests that topical NSAIDs may be more effective than systemic NSAIDs for a preventive postoperative pain management strategy following PRK. While the pathophysiology behind lower pain scores in the topical group is unknown, one theory could be a more direct and concentrated dose to the site of the sensory nerves affected compared to the oral route.

As this study is unmasked, patient awareness of treatment type could affect subjective pain scores and therefore creates a potential limitation. Although the optional use of oral hydrocodone-acetaminophen 5–325 mg for breakthrough pain was allowed, this did not differ statistically between study groups, and the percentage of use was low in both groups. This study also did not assess the systemic effect of oral NSAIDs, but our patients reported none. Patients were instructed to identify peak pain scores during the five days following the procedure, but did not specifically record the exact time of the peak pain during each day. As Sobas et al have shown, pain is reported as soon as 30 minutes after the procedure and increases in the next eight to nine hours, therefore the lack of specific data regarding timing is an additional weakness of our study.[23] Peak pain was higher in the oral NSAID group on day two but not much different on day three. It is possible that if patients were pre-treated with oral NSAIDs beginning 24 hours before surgery, perhaps pain relief in this group would be better on day 2. Finally, as is common practice for many PRK practitioners, the combined prophylactic use of both oral and topical NSAIDs might be more effective.

Conclusion

In conclusion, twice-daily oral naproxen sodium 220 mg was inferior to twice-daily topical ketorolac 0.4% in the treatment of early postoperative pain after PRK. Topical NSAIDs avoid the potential systemic side effects and drug interactions of oral NSAIDs but may cause serious ocular side effects and are more expensive. This study also identified a consistent, identifiable trend in the postoperative pain course in which pain scores were highest on days two and three and this may allow for better patient counseling and pain management or prevention for PRK.

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Disclosure

No author has a financial or proprietary interest in any material or method mentioned.

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