

Update: Do Ophthalmic Nonsteroidal Anti-Inflammatory Drugs Reduce the Pain Associated With Simple Corneal Abrasion Without Delaying Healing?

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Introduction: Some studies have suggested that ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs) decrease the pain associated with corneal abrasions without impairing healing. This evidence-based emergency medicine (EBEM) critical appraisal reviews the literature, including additional studies appearing since the publication of an earlier EBEM review in 1999.

Methods: The updated search for randomized controlled trials from 1999 to 2002 complemented the previous 1966 to 1999 search. The methodologic quality of the studies was assessed. Qualitative methods were used to summarize the study results.

Results: The search identified 3 studies not included in the previously published review of ophthalmic NSAIDs, yielding a total of 5 blinded, randomized, placebo-controlled trials involving NSAIDs for corneal abrasions. The methodologic quality of the new studies was somewhat higher than that of the 2 original studies and was rated as "good" to "strong." The qualitative summary indicates that NSAIDs provide greater pain relief and improvement of other subjective symptoms when compared with placebo. However, whether the reduction of pain, as measured by visual analog pain scales, exceeds the minimal clinically significant difference is equivocal. The use of ophthalmic NSAIDs may decrease the need for sedating analgesics.

Conclusion: Ophthalmic NSAIDs appear to be useful for decreasing pain in patients with corneal abrasions who can afford the medication and who must return to work immediately, particularly where potential opioid-induced sedation is intolerable.

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In 1999, Brown et al¹ published an evidence-based emergency medicine (EBEM) review of the efficacy of ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs) to reduce the pain associated with simple corneal abrasions. We performed an updated review on this topic using the methods described by the original authors.

We searched MEDLINE, using the Ovid interface, between January 1, 1999, and April 2002 using the search strategy and selection criteria previously described.¹ We identified 4 randomized controlled trials²⁻⁵ that were not considered in the original review but that fulfilled the authors' inclusion criteria (Figure). We also screened the bibliographies of the 4 articles and found no additional relevant studies.

We searched the Cochrane Database of Systematic Reviews on the Ovid search engine for systematic reviews evaluating ophthalmic NSAIDs in the treatment of corneal abrasions. Our search terms were "cornea or eye injuries or ophthalmic NSAID," which identified 11 articles, none of which were relevant. The same search on the Cochrane DSR, ACP Journal Club, and DARE database was also negative. On searching the Cochrane

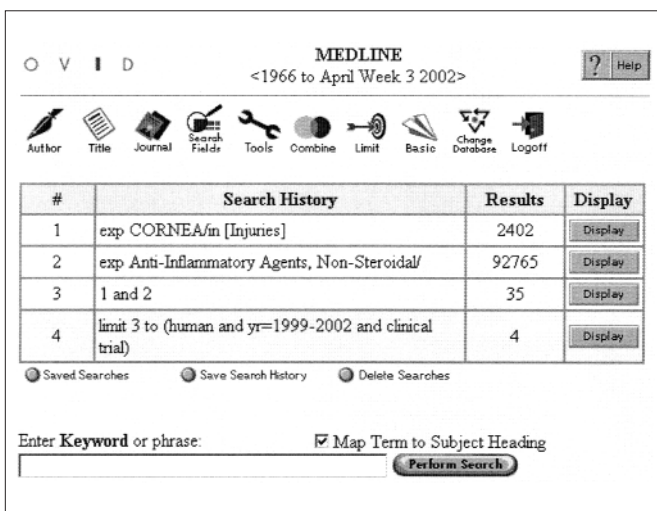
Controlled Trials Registry, we identified 4 of the 5 studies included in this review using the single search term "corneal abrasions." The study by Alberti et al² was not identified.

Patrone et al⁴ studied the use of indomethacin 0.1% NSAID drops in patients with traumatic corneal abrasions. Patients were randomized to treatment either with or without indomethacin. Neither investigators nor research subjects were masked to treatment allocation. Among the cointerventions, the investigators included the use of soft contact lenses for 24 hours in all patients. Because of the use of contact lenses as a cointervention, we excluded this study from further review. A total of 5 studies therefore meet the inclusion criteria of the original review¹; they are summarized in the Table.^{2,3,5-7}

Alberti et al² studied the use of an ophthalmic solution containing a fixed combination of indomethacin 0.1% and gentamicin sulfate compared with gentamicin sulfate alone in 123 patients with traumatic corneal abrasions. Patients were randomized, and the study was double-masked. The participants completed a visual analog scale (VAS) at 5 intervals during the 4- to 5-day study period. Although control subjects on average had deeper corneal abrasions and reported a higher global score for associated symptoms, the 2 groups had similar baseline pain scores. Eye patching was allowed if pain was "unbearable." Research subjects were given either indomethacin 0.1% combined with gentamicin eye-drops or gentamicin eyedrops alone, which they were instructed to instill 4 times a day for 5 to 6 days. Of the initial 123 patients, 111 were followed up to completion. The investigators found a statistically significant pain reduction at all measured times in the indomethacin group. At 1 hour posttreatment, patients receiving indomethacin had a mean pain intensity reduction ($P=.007$ for comparison between the 2 groups). There was no statistically significant difference in associated symptoms or in the number of patients taking supplemental analgesics. Four patients in each group took paracetamol for pain rescue. There was no difference in time to healing. Four adverse events led to treatment discontinuation, 3 in the study group and 1 in the control group.

Figure.

MEDLINE search conducted April 2002 using the Ovid search engine. The screen icons above "Search History" allow combining and limiting of searches, as well as the searching of medical databases other than MEDLINE.



Goyal et al³ studied the use of ketorolac trometanol 0.5% NSAID solution in 85 patients with traumatic corneal abrasions or foreign body removal compared with placebo artificial tears (Liquifilm). The practice setting is poorly described, and the applicability of the

results to emergency care settings is potentially open to question. Patients were randomized to treatment groups in this double-masked study and were followed up daily until healing was complete. All patients were asked at presentation to complete a questionnaire that

Table.

Summary of 5 studies of ophthalmic NSAIDs for corneal abrasions, including 2 appraised in a previous review.¹

Study Characteristic	Kaiser and Pineda ⁶ (1997) (N=100)	Jayamanne et al ⁷ (1997) (N=40)	Alberti et al ² (2001) (N=123)	Goyal et al ³ (2001) (N=85)	Szucs et al ⁵ (2000) (N=49)
NSAID ophthalmic solution	Ketorolac 0.5% 4 times daily	Diclofenac 0.1% 4 times daily	Indomethacin 0.1% (combined with gentamicin) 4 times daily	Ketorolac 0.5% 4 times daily	Diclofenac 0.1% every 6 h while awake
Population	Eye and ear infirmary in the United States	Eye casualty department in United Kingdom	Six centers in France and Portugal	Ophthalmology practice in Wales; patients with abrasions (72%) or foreign body removal (28%) of <48 h duration	Community-based US ED
Comparison group(s)	"Control vehicle"	Normal saline solution	No indomethacin	Liquifilm tears	Natural Tears
Outcome measures	Scale of 0–10 (0 representing no pain and 10 representing severe pain); "reviewed daily" plus outpatient diary	VAS of 0–100 mm and a categoric pain scale; "reviewed daily" until complete corneal reepithelialization occurred	VAS of 0–100 mm at 5 intervals; follow-up day 1 and 4 or 5	VAS of 0–5 cm; daily return visits until complete healing	NPIS of 0–10 cm; telephone at both 2 hours and within 10 days; outpatient diary; return visit at 24–36 h
Results					
Pain intensity	Patients receiving ketorolac had a mean pain intensity reduction at 24 h of 2.7 compared with 1.4 in control subjects (<i>P</i> =.002; CIs not given)	Patients receiving diclofenac experienced significant reduction in pain on day 1 (less on day 2) by both VAS and categoric pain scales; pain score data not provided	Patients receiving indomethacin had a mean pain intensity reduction at 1 h of 15.7 mm compared with 9.8 mm in control subjects (<i>P</i> =.007 for comparison)	Patients receiving ketorolac had a mean pain intensity reduction at 24 h of 26 mm compared with 24 mm in control subjects; clinically and statistically insignificant	Patients receiving diclofenac had a mean pain intensity reduction at 2 h of 3.1 cm compared with 1.0 cm in control subjects (difference 2.1 cm; 95% CI 0.8 to 3.4); data incomplete after 2 h
Subjective symptoms	Fewer patients receiving ketorolac had photophobia and foreign body sensation on day 1 compared with control subjects	Patients receiving ketorolac experienced foreign body sensation and photophobia less frequently	No significant difference	No significant difference	Not reported
Return to work	Patients receiving ketorolac had significantly earlier return to work	Not reported	Not reported	Not reported	Not reported
Supplemental oral analgesics	Not reported	Not reported	4 patients in each group took paracetamol in the 24 hours after starting the study treatment; 1 in the study group took paracetamol with codeine	16% of ketorolac group took rescue medication compared with 50% of control subjects (difference 34%; 95% CI 15% to 53%)	20% of diclofenac group took rescue medication compared with 42% of control subjects (difference 22%; 95% CI -4% to 47%)
Time to healing	No significant difference	Not reported	No difference	No difference	Not reported

included a somewhat atypical VAS of 0 to 5 (0 being no symptoms, 5 being worst symptoms). The authors provided no further details regarding the measurement instrument. Of an initial 88 patients, 3 were ultimately excluded from the study. The groups were similar at the beginning of the trial. Patients were released with a masked bottle of either ketorolac trometanol 0.5% or placebo, which they were instructed to instill 4 times a day until the abrasion healed. Cointerventions administered to both groups included cycloplegics (cyclopentolate 0.5%) at the initial visit and chloramphenicol eye ointment 4 times daily for 24 hours. Oral analgesics were permitted, and the amounts were reported. Patients receiving ketorolac had a clinically and statistically insignificant pain reduction at 24 hours compared with patients in the control group ($P=.76$ for comparison between the 2 groups). There was no statistically significant difference in associated symptoms. However, there was an important decrease in the number of patients receiving ketorolac using supplemental oral analgesics. There was no difference in the rate of healing in either group, and no patients in either group had adverse events at 24 hours.

Szucs et al⁵ compared diclofenac 0.1% ophthalmic NSAID solution to a control vehicle (Natural Tears) in 49 patients with corneal abrasion. The treatment assignment was randomized, and the study drugs were double-masked. Baseline characteristics of the 2 groups were similar. In the emergency department, patients were treated with a topical anesthetic (proparacaine hydrochloride 0.5% solution), 2 drops of a topical antibiotic (gentamicin 0.3% solution), and either diclofenac or the control vehicle. Some patients also received 1 drop of a cycloplegic (cyclopentolate) at the discretion of the treating physician. Patients were discharged with a masked bottle of either diclofenac or the control vehicle (Natural Tears), with instructions to instill 1 drop every 6 hours while awake for 24 to 36 hours. Patients also received a bottle of topical gentamycin with instructions to instill 2 drops every 2 hours while awake for 24 hours. All patients were given rescue analgesics in the form of 3 tablets containing 5 mg of oxycodone and 325 mg of acetaminophen, in addition to a prescription for

10 more tablets. One control subject had incomplete follow-up. Patients completed a pain diary that reported the amount of rescue medication taken, as well as Numeric Pain Intensity Scale scores and were followed up to study completion. The authors reported a significantly greater improvement in the 2-hour mean Numeric Pain Intensity Scale score in the diclofenac group compared with the control group ($P=.002$). Patients in the diclofenac group were only half as likely to take oxycodone-acetaminophen rescue medication (20% versus 42%), although the 95% confidence interval (CI) for the difference includes the possibility of greater use in the diclofenac group. There were no adverse events noted other than transient mild stinging.

These 3 randomized trials, combined with the 2 trials included in the original review of ophthalmic NSAIDs, support the use of these agents as analgesics for acute corneal abrasion. All 5 trials were randomized and double-blinded, and except for the study by Alberti et al,² in which patients in the control group had more severe abrasions and a higher global score for associated symptoms, the groups were well balanced at the start of the trial. Follow-up rates ranged from 88% to 100% and were more than 90% in all but 1 study. Cointerventions were variable but were equally administered in the individual trials.

Important differences among these studies in both the timing and means of assessing pain reduction in treatment and control groups render a statistical pooling of their results inappropriate. It is therefore necessary for the clinician to settle for a qualitative summary of the evidence to date. All 5 studies reported a reduction in pain intensity of variable clinical and statistical significance compared with controls in patients treated with ophthalmic NSAIDs. As noted in the original review,¹ a change of 1.3 cm on a 10-cm VAS has been empirically perceived by patients to be a clinically important difference. Three of the 5 studies of ophthalmic NSAIDs^{2,5,6} reported complete data on pain reduction measured by means of a 10-cm VAS at least one point in time after administration of the study drug. Of these, only 2^{5,6} report a difference between the study groups of this magnitude or larger and in neither case

did the 95% CI around the difference exclude a value below this threshold. Fewer patients in the treatment group reported subjective symptoms in 2 of the studies.^{6,7} One study reported significantly earlier return to work.⁶ Two of the 3 studies that reported analgesic use^{3,5} observed a decrease in the use of supplemental analgesia. No study identified a change in time to healing, and no serious adverse events or serious infections occurred in the treatment groups.

Although these data support the use of ophthalmic NSAIDs in the treatment of pain from corneal abrasion injuries, the results of these trials must be translated to the individual patient in a given practice locale. Ophthalmic NSAIDs have not been compared with oral opioids alone or to oral NSAIDs. In addition, ophthalmic NSAIDs are more expensive than these alternative oral analgesics. In clinical practice, the evidence gained from clinical trials must be placed in the context of clinician experience. The clinician must also consider a patient's values, preferences, and rights. Can the patient afford an ophthalmic NSAID? Is there a compelling reason to prescribe NSAID eye drops over an oral analgesic? Does the patient need to return to work immediately? Patients who can afford the medication, must return to work immediately, and for whom potential opioid-induced sedation is intolerable are the most likely candidates for the administration of ophthalmic NSAIDs during the first 24 hours after a traumatic corneal abrasion.

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Critically Appraised Topic (CAT):

“Do ophthalmic nonsteroidal anti-inflammatory drugs reduce the pain associated with simple corneal abrasion without delaying healing?”

Question	In patients with acute corneal abrasions treated in the acute care setting, will ophthalmic NSAIDs decrease pain as well as or better than placebo, oral analgesics, or standard therapy without impairing healing?
Reviewed by	Weaver CS, Terrell KM
Date	August 16, 2002
Expiration date	August 16, 2004
Clinical bottom line	Ophthalmic NSAIDs appear to be useful for decreasing pain in patients with corneal abrasions who can afford the medication and who must return to work immediately, particularly where potential opioid-induced sedation is intolerable. Since the previously published EBEM review of ophthalmic NSAIDs, 3 additional studies demonstrated greater pain relief and improvement of other subjective symptoms when compared with placebo. The clinical significance of pain reduction from these agents, as measured by visual analogue pain scales, is borderline. They may decrease the need for sedating analgesics.
Search strategy	MEDLINE was searched by way of the Web-based Ovid search engine: explode “Cornea/in [Injuries]” AND explode “Anti-inflammatory agents, non-steroidal” (as medical subject heading [MeSH] terms); limited to “human” and “clinical trials” from years 1999 to 2002.
Citations	<ol style="list-style-type: none"> 1. Alberti MM, Bouat CG, Allaire CM, et al. Combined indomethacin/gentamicin eyedrops to reduce pain after traumatic corneal abrasion. <i>Eur J Ophthalmol.</i> 2001;11:233-239. 2. Goyal R, Shankar J, Fone DL, et al. Randomised controlled trial of ketorolac in the management of corneal abrasions. <i>Acta Ophthalmol Scand.</i> 2001;79:177-179. 3. Szucs PA, Nashed AH, Allegra JR, et al. Safety and efficacy of diclofenac ophthalmic solution in the treatment of corneal abrasions. <i>Ann Emerg Med.</i> 2000;35:131-137. 4. For the original review of this topic and the appraisal of 2 earlier studies, see <i>Ann Emerg Med.</i> 1999;34:526-534.
Study characteristics	<p>Study population</p> <p>Alberti et al: 123 outpatient adults >18 years old with traumatic corneal abrasion or requiring ablation of a superficial corneal foreign body and/or curettage. Excluded if previous intolerance to study drug, systemic analgesia within 24 hours, anti-inflammatory treatment within 5 days, contact lens wearer, chemical abrasions, other signs of ocular trauma, deep corneal lesion beyond anterior stroma, or monophthalmia.</p> <p>Goyal et al: 85 adults ages 16–80 years with corneal abrasion or foreign body removal <48 hours without any prior treatment. Excluded if contact lens wearer, signs of infiltration or infection, erosion more than one third of corneal surface, or previous corneal surface disease.</p> <p>Szucs et al: 49 adults ≥18 years with traumatic corneal abrasions and a minimum pain intensity score >3. Excluded if recent eye surgery, glaucoma, ocular infection, other signs of ocular trauma, adverse reactions to diclofenac or NSAIDs including aspirin, any narcotic use within 6 hours, pregnancy or breast feeding, or if unavailable for telephone follow-up at 2 hours.</p> <p>Interventions</p> <p>Alberti et al: Combined indomethacin 0.1%/gentamicin eyedrops versus gentamicin eyedrops alone instilled 4 times a day for 5 to 6 days, and oral analgesics (paracetamol).</p> <p>Goyal et al: Ketorolac trometanol 0.5% or placebo instilled 4 times a day until healed, initial dose of cyclopentolate 0.5%, chloramphenicol eye ointment 4 times a day for 1 day, and oral analgesics.</p> <p>Szucs et al: Diclofenac sodium 0.1% or placebo instilled every 6 hours while awake for 24 to 36 hours, gentamicin 0.3% solution every 2 hours while awake for 24 hours, and rescue analgesia (oxycodone with acetaminophen).</p> <p>Outcome measures</p> <p>Alberti et al: Continuous visual analogue pain scale (0–100 mm). Photophobia, tearing, burning, irritation, and foreign body sensation were rated on a severity scale of 0–3. Conjunctival hyperemia and ciliary injection were assessed by the treating physician using the same 0–3 scale. Surface area of corneal abrasion was measured at each visit. All use of systemic analgesics was recorded.</p> <p>Goyal et al: Subjective symptoms of pain, photophobia, grittiness, watering, and blurring of vision on a VAS of 0–5. The need of any additional oral analgesics, duration of pain, and effect on sleep were also assessed. Patients examined daily for size of epithelial defect, anterior segment inflammation and the presence of any complications.</p> <p>Szucs et al: 10-cm numbered Numeric Pain Intensity Scale. Use of oxycodone-acetaminophen.</p>
Critical appraisal	<p>Alberti et al: Randomized, double masked with 88% follow-up. Groups similar except control group had deeper corneal abrasions and higher global score for associated symptoms. Both groups had similar initial pain intensities. Use of additional analgesics reported. It is unclear if an intention-to-treat analysis was performed. Quality rating: “good.”</p> <p>Goyal et al: Randomized, double masked with 97% follow-up. Groups similar at start of trial. Use of additional analgesics reported. An intention-to-treat analysis was performed. Quality rating: “good.”</p> <p>Szucs et al: Randomized, double masked with 98% follow-up. Groups similar at start of trial except for sex. Use of additional analgesics reported. Intention-to-treat analysis apparently followed. Quality rating: “strong.”</p>

Continued on p. 140.

Critically Appraised Topic (CAT) (continued):

Results

Alberti et al: Patients receiving indomethacin had a mean pain intensity reduction at 1 hour of 15.7 mm compared with 9.8 mm in control subjects ($P=.007$ for comparison between the 2 groups). There was no statistically significant difference in associated symptoms or number of patients taking supplemental analgesics.

Goyal et al: Patients receiving ketorolac had a reduction of 26 mm at 24 hours compared with 24 mm in control subjects ($P=.76$ for comparison between the 2 groups). There was no statistically significant difference in associated symptoms. Significantly fewer (16% versus 50%) patients in the treatment group took supplemental analgesics (absolute difference 34%; 95% CI 15% to 53%).

Szucs et al: Patients receiving diclofenac had a mean NPIS reduction of 31 mm at 2 hours compared with 10 mm in control subjects (absolute difference 2.1 cm; 95% CI 0.8 to 3.4). Associated symptoms were not reported. There was a clinically significant reduction (20% versus 42%) in use of supplemental analgesics in the diclofenac group (absolute difference 22%; 95% CI: -4% to 47%).
