

Short-Term Topical Tetracaine Is Highly Efficacious for the Treatment of Pain Caused by Corneal Abrasions: A Double-Blind, Randomized Clinical Trial

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Study objective: The objective of this study is to show that patients with corneal abrasions would experience more pain relief with short-term topical tetracaine than placebo.

Methods: The study was a prospective, double-blind, randomized trial of tetracaine versus placebo set in the emergency department (ED). A total of 118 adults who presented with uncomplicated corneal abrasions were included and randomized. The intervention was either topical tetracaine or placebo applied every 30 minutes as needed for 24 hours. The primary outcome was the overall numeric rating scale pain score measured at the 24- to 48-hour ED follow-up examination.

Results: One hundred eleven patients were included in the final analysis, 56 in the tetracaine group and 55 in the placebo group. At the 24- to 48-hour follow-up, the overall numeric rating scale pain score after use of the study drops was significantly lower in the tetracaine group (1) versus placebo group (8) ($\Delta 7$; 95% confidence interval 6 to 8). Patients in the tetracaine group used less hydrocodone than those in the placebo group. The complication rates between the 2 groups were similar.

Conclusion: Short-term topical tetracaine is an efficacious analgesic for acute corneal abrasions, is associated with less hydrocodone use compared with placebo, and was found to be safe in this sample. [Ann Emerg Med. 2020;■:1-7.]

Please see page XX for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Corneal abrasions are among the most common eye-related injuries treated in the emergency department (ED).¹ Topical anesthetic drops are routinely used before slit-lamp examination for diagnosis of corneal abrasions and often provide immediate pain relief. Patients are then discharged with oral analgesics and topical antibiotics. The use of topical anesthetics for outpatient treatment of corneal abrasions is discouraged by most emergency medicine textbooks because of concerns over safety. Case reports of abuse and misuse, as well as animal studies, have suggested that long-term use of topical anesthetics may lead to rare complications.²⁻⁹

Importance

More recently, the ophthalmology literature has challenged this dogma, demonstrating the safety and

efficacy of topical anesthetics for postoperative pain after photorefractive keratectomy surgery. Two clinical trials showed no delayed healing after a short course of topical anesthetics after photorefractive keratectomy surgery.^{10,11} Whether this could be applied to nonsurgical patients in the ED was investigated by 2 small clinical trials that showed similar efficacy and safety but were underpowered to prove a statistical difference.^{12,13} In 2014, a larger randomized trial demonstrated the safety of tetracaine for ED patients with corneal abrasions but failed to show a significant difference in patient visual analog scale (VAS) pain ratings over time.¹⁴ More recently, a retrospective cohort study of 444 ED patients given tetracaine for 24 hours reported no serious complications or uncommon adverse events.¹⁵ If topical anesthetics could be safely prescribed for short-term use in the management of corneal abrasions, it might decrease use of systemic opioids for this purpose.

Editor's Capsule Summary*What is already known on this topic*

Corneal abrasions can be extremely painful.

What question this study addressed

How effective is home use of topical tetracaine every 30 minutes as needed for 24 hours?

What this study adds to our knowledge

In this randomized, placebo-controlled trial of 111 adults, patients' median pain scores for the first 24 to 48 hours overall were 1 of 10 with tetracaine and 8 of 10 with placebo, with fewer hydrocodone tablets ingested (median 1 versus 7). There were no serious adverse events.

How this is relevant to clinical practice

Patient home use of topical tetracaine for corneal abrasions for up to 24 hours was efficacious, was opioid sparing, and appears safe, although larger observational studies would be required to rule out rare adverse events.

Goals of This Investigation

The aim of this randomized, double-blind trial was to compare the effectiveness of topical tetracaine versus placebo in ED patients with corneal abrasions as measured by their numeric rating scale (NRS) pain score at their 24- to 48-hour ED follow-up examination.

MATERIALS AND METHODS**Study Design**

This was a prospective, randomized, double-blind, placebo-controlled trial to determine the effect of topical tetracaine for ED patients with corneal abrasions. Approval was obtained from our institutional review board before commencement. The study began in January 2015 and continued through September 2017. This trial is reported in accordance with Consolidated Standards of Reporting Trials guidelines.

Setting

This study was performed at an urban community ED with an associated emergency medicine residency program in Oklahoma City, OK, with a census of 86,000 visits per year. Patients were prospectively enrolled by their attending physician or resident emergency physician. All physicians were informed of the study protocol and inclusion and exclusion criteria, and trained in the enrollment of patients.

Selection of Participants

Patients were eligible for enrollment if they were aged 18 to 80 years, presented to the ED with suspected acute corneal abrasion, and gave written informed consent. Patient enrollment into the study could occur at any time during the day or night, 7 days a week. Patients were excluded if they wore contact lenses, had had previous corneal surgery or transplant in the affected eye, presented more than 36 hours after their injury, had a grossly contaminated foreign body, or had coexisting ocular infection. Additional exclusion criteria were pregnancy, retained foreign body, penetrating eye injury, immunosuppression, allergy to study medication, inability to attend follow-up, inability to fluently read and speak English or Spanish, or any injury requiring urgent ophthalmologic evaluation (large or complicated abrasions with vision loss, corneal ulcers, or corneal lacerations). Data were collected on all patients who declined study participation or met any exclusion criteria.

Interventions

Eligible patients were randomized in a 1:1 ratio to receive tetracaine or placebo. The allocation list was generated by a computer random-number generator and randomization was performed with numbered, sealed, opaque envelopes issued in sequential order to the physician enrolling the patient in the study. Enrolling physicians were blinded to the randomization plan and obtained a numbered sealed envelope from the ED Pyxis. Each envelope contained both an antibiotic ophthalmic solution (polymyxin B sulfate/trimethoprim sulfate) with instructions to instill 2 drops every 4 hours into the affected eye and the tetracaine or placebo with instructions to apply 1 drop every 30 minutes as needed for pain for a maximum of 24 hours. The placebo consisted of 4 separate 0.5-mL ampules of a balanced artificial tear solution (Systane; Alcon, Fort Worth, TX), whereas the tetracaine 0.5% was packaged in a single 2-mL bottle. The envelopes were opaque to ensure enrolling physicians remained blinded despite the different packaging of the placebo and the tetracaine. The placebo and tetracaine were labeled for the patient as the "study drops" to maintain blinding. In addition to the medications contained in the envelope, all study participants received a prescription for hydrocodone/acetaminophen 7.5/325 mg number 12 and were instructed to use 1 or 2 tablets as needed every 6 hours for breakthrough pain.

Data Collection and Processing

All baseline data, including age, sex, initial NRS pain score, mechanism of injury, and language spoken, were

collected and recorded. Patients were asked to record pain score measurements on a standard NRS (from 0 to 10 cm) before and 2 minutes after each use of the study drops. Patients also recorded the amount of hydrocodone ingested between enrollment and their follow-up ED visit. Patients were reassessed at 24 to 48 hours by an emergency physician who was blinded to group allocation and performed and documented findings of repeated slit-lamp examination. Persistence of the corneal abrasion and any evidence of delayed healing or complication were documented. Additionally, patients were asked by the physician to rate their overall NRS pain score after using the study drops. Patients were not administered drops at this time, but were asked to give their overall impression of their pain after drop use. Any patients found to have a significant complication were immediately referred to the study ophthalmologist, who was also blinded to the patient's group allocation. The study drops were collected and disposed of to ensure no patients used them for a longer period. The patients were asked to follow up with the study ophthalmologist within 1 week of their initial visit. If patients did not follow up with the study ophthalmologist, they were contacted by telephone at the conclusion of the study. Patients were asked about any persistent symptoms or repeated visits to any health professional that were related to their initial corneal abrasion. At the conclusion of the study, we performed an electronic medical record search of all enrolled patients for repeated visits related to their initial corneal abrasion.

Outcome Measures

The primary endpoint of the study was the overall NRS pain score measured at the patient's initial follow-up ED visit. Secondary endpoints were the amount of hydrocodone ingested for breakthrough pain, and any adverse events.

Primary Data Analysis

Descriptive statistics are reported as medians with interquartile ranges and proportions with exact binomial 95% confidence intervals (CIs). Wilcoxon signed rank test was used for the primary comparison. We entered data without patient identifiers into a custom database constructed in Microsoft Excel (version 14.0.7140.5002; Microsoft) and performed analysis with the statistical add-on package Analyze-it (version 2.26; Excel 12+; Microsoft).

Calculations indicated that a sample of approximately 60 patients per group would have 95% power (at the 0.05

level) to detect a minimum clinical difference in pain scores of 1.5 cm on a 10-cm NRS, given an SD of 2.5 cm.

Data for all participants who underwent random assignment were analyzed according to group assignment in an intention-to-treat fashion.

RESULTS

Characteristics of Study Subjects

Figure 1 demonstrates the enrollment of patients. In the tetracaine group, 3 patients did not attend the ED follow-up visit and 45 did not return for their 1-week follow-up with the study ophthalmologist. Of these 48 patients who did not complete all follow-up, 16 responded to a text message, reporting no study-associated complications. In the placebo group, 4 patients did not attend the ED follow-up visit and 45 did not return for their 1-week follow-up with the study ophthalmologist. Of these 49 patients who did not complete all follow-up, 6 responded to a text message, reporting no study-associated complications.

The baseline characteristics of the 118 patients are reported in Table 1. The baseline pain scores before enrollment were similar between the 2 groups. All patients whose data were analyzed in both groups reported compliance with using at least one drop of the study drug and logged their NRS pain scores before and after use.

Main Results

At the 24- to 48-hour follow-up, the overall NRS pain score after use of the study drops was significantly lower in the tetracaine group (1 versus 8) compared with that of patients in the placebo group (difference=7; 95% CI 6 to 8; $P<.001$) (Figure 2). Table 2 summarizes the results for the primary and secondary outcomes. Table 3 demonstrates the complications and outcomes of all patients enrolled. There was a greater difference between the patients' overall NRS score compared with their baseline pain score in the tetracaine group (6; 95% CI 5 to 7) versus the placebo group (0; 95% CI 0 to 0). The tetracaine group reported using the study drops more times (9 versus 5) than the placebo group (difference=4; 95% CI 2 to 5). The number of patients found to have a small residual corneal abrasion on their repeated ED slit-lamp examination was similar between groups, 10 of 56 (18%) in the tetracaine group and 6 of 56 (11%) in the placebo group (95% CI -6.4 to 20.4).

LIMITATIONS

First, this study was not powered to establish safety for rare adverse events that could be associated with topical anesthetic use. To demonstrate safety, a much larger sample

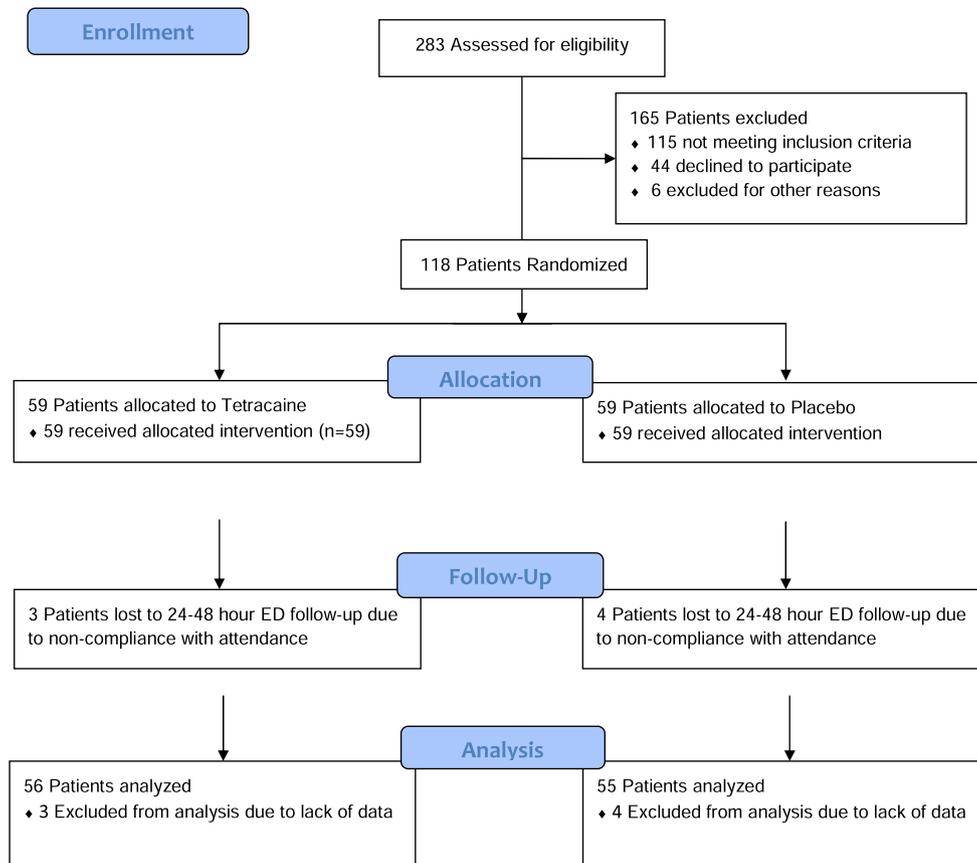


Figure 1. Consolidated Standards of Reporting Trials flowchart of the study.

size would be needed. Second, although we attempted to blind patients from their allocation group, the burning nature of the tetracaine may have unintentionally unblinded the patients. We did not specifically ask the patients whether they knew what group they were assigned to, and this could have biased our outcomes. Additionally,

Table 1. Baseline clinical and demographic characteristics.*

Group	Tetracaine, n = 59	Placebo, n = 59
Age, y	35 (28–43)	38 (27–47)
Male patients, No. (%)	36 (61)	34 (58)
Baseline pain rating	7 (6–7.5)	7 (6–8)
Mechanism, No. (%)		
Metallic foreign body	8 (14)	5 (9)
Other foreign body	17 (29)	15 (25)
Direct trauma	11 (17)	20 (34)
Unknown	23 (40)	19 (32)
Language, No. (%)		
English	57 (97)	57 (97)
Spanish	2 (3)	2 (3)

*Results are expressed as median (interquartile range) unless otherwise indicated.

patients may have been unblinded as a result of the placebo's having been packaged in 4 ampules versus the tetracaine in a single bottle. Third, we excluded patients with large or complicated corneal abrasions, penetrating eye injuries, contact lens wearers, and patients with previous corneal surgery in the affected eye. We also excluded patients presenting more than 36 hours after their injury and those with grossly contaminated foreign bodies or coexisting ocular infection. Our findings would not be generalizable to patients with any of these more complicated conditions. Fourth, this study was performed at a single center, giving it limited external validity. Fifth, very few patients in either group (20% in tetracaine and 18% in placebo) attended their 1-week follow-up with the study ophthalmologist. We hypothesize that because corneal abrasions have a relatively rapid healing period, most patients in both groups were asymptomatic 1 week later and thus did not heed the importance of the second follow-up visit. It is possible that complications were missed or developed later, which we attempted to discover through subsequent telephone contact, electronic medical record search, or both. However, it is possible that patients sought care at other locations and complications may have

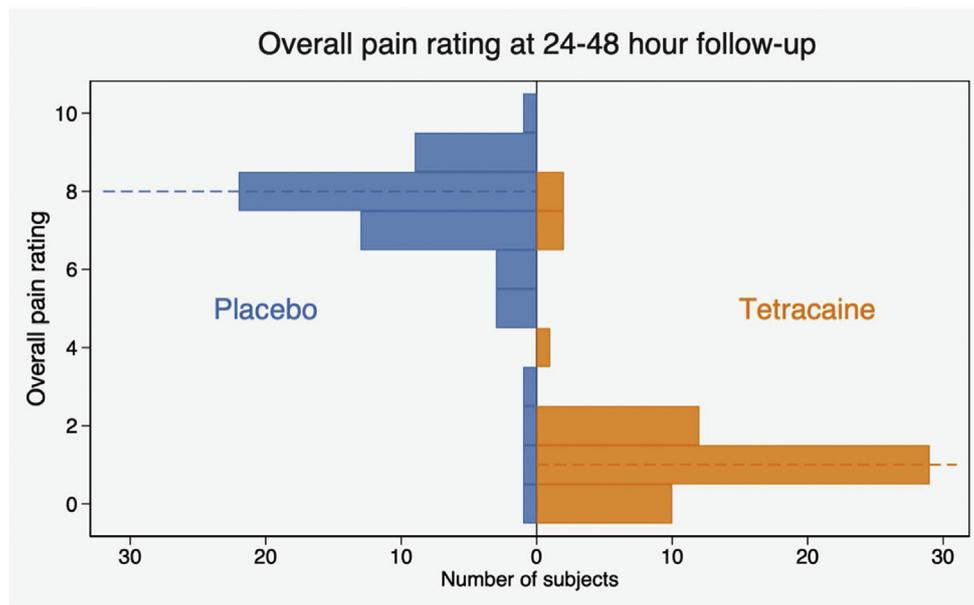


Figure 2. Overall pain rating at 24- to 48-hour follow-up.

been missed. Nonetheless, the data needed for our primary and secondary endpoints were collected at the initial ED follow-up, with 95% of patients in the tetracaine group and 93% in the placebo group attending that visit.

DISCUSSION

In this randomized, double-blind study of patients with corneal abrasions, topical tetracaine resulted in significantly lower NRS pain scores at 24 to 48 hours compared with placebo. In addition, patients given tetracaine ingested fewer opiates for breakthrough pain, without any increase in complication rates. These data suggest tetracaine is an efficacious therapy for ED patients with corneal abrasions.

Waldman et al¹⁴ performed a randomized trial that did not show a significant reduction in VAS pain scores with tetracaine versus placebo. In this prior study, the primary outcome was safety and corneal healing instead of VAS pain scores. Therefore, many patients were included in the

study even if they did not return their pain questionnaires. Moreover, patients were also instructed to record their pain scores every 2 hours instead of 2 minutes after use of the study drug, when it is most effective. These investigators found a significant reduction in NRS pain scores in the tetracaine group at 1 week.

Although they conducted a smaller randomized controlled trial, Ball et al¹³ had similar findings of significantly reduced VAS pain scores in patients receiving dilute proparacaine. They also reported less overall opiate use in the proparacaine group, although it was not statistically significant.

There are 2 published studies reviewing the safety of short-term topical anesthetics for the treatment of simple corneal abrasions. A systematic review in 2015 found no adverse outcomes from use of topical anesthetics in the treatment of corneal abrasions for postoperative photorefractive keratectomy patients, as well as ED patients.¹⁶ In 2017, a large retrospective cohort study

Table 2. Summary results for each study group.*

Endpoint	Tetracaine (n=56)	Placebo (n=55)	Difference (95% CI)
Primary endpoint			
Overall NRS score at 24- to 48-h follow-up	1 (1 to 2)	8 (7 to 8)	7 (6 to 8)
Secondary endpoint			
No. of hydrocodone tablets recorded	1	7	6 (4 to 9)
Adverse events, No. (%)	3.6	11	7.4 (-2.9 to 18.6)

*Results are expressed as median (interquartile range) unless otherwise indicated.

Table 3. Patients with any complication.

Complication	Outcome
Tetracaine group (n=2)	
Worsening corneal abrasion on ED follow-up examination; patient immediately referred to study ophthalmologist	Additional diagnosis of allergic conjunctivitis made; normal healing by 10 days
Worsening corneal abrasion on ED follow-up examination; patient immediately referred to study ophthalmologist	Additional diagnosis of acute iritis made; prescribed steroid drops, with normal healing by 10 days
Placebo group (n=6)	
Worsening corneal abrasion on ED follow-up examination; patient immediately referred to study ophthalmologist	Additional diagnosis of traumatic uveitis made; normal healing by 10 days
Multiple repeated ED visits for eye pain found on EMR review; referral to study ophthalmologist after fourth visit	Uncomplicated corneal abrasion with punctate keratitis; normal healing by 7 days
Returned to ED the same day, with residual foreign body (eyelash) removed in ED	No further treatment required by ophthalmologist; normal healing by 7 days
Retained metallic foreign body observed on ED follow-up examination; patient immediately referred to study ophthalmologist	Foreign body removed; residual rust ring with normal healing by 10 days
Worsening corneal abrasion on ED follow-up examination; patient immediately referred to study ophthalmologist	No further treatment required by ophthalmologist; normal healing by 7 days
Persistent redness and blurry vision on ED follow-up examination; patient immediately referred to study ophthalmologist	No further treatment required by ophthalmologist; normal healing by 7 days

found no evidence that 24-hour use of topical tetracaine for simple corneal abrasions diagnosed in the ED was unsafe.¹⁵

Uncomplicated corneal abrasions are commonly observed and treated in the ED. Even minor corneal abrasions can cause considerable pain as a result of the cornea's vast innervation. Emergency physicians should aim to provide adequate analgesia in the safest manner possible. In our current study, to our knowledge the largest randomized controlled trial to date, we found topical tetracaine to be effective, and it appears safe for short-term use in treating corneal abrasions diagnosed in the ED. We found a 6.1-point reduction in the overall NRS pain score at 24 to 48 hours versus that in the placebo group. We also found that the tetracaine group recorded use of the study drops significantly more, further demonstrating the efficacy of topical anesthetics in the treatment of pain from corneal abrasions.

The United States is currently in the midst of an opioid crisis, with substantial increases in opioid use disorder, as well as fatal and nonfatal opiate overdoses, reported during the last few decades. Even a single opiate prescription for acute pain from the ED can lead to subsequent prescriptions for opiates and opioid use disorder.¹⁷ We found that patients in the tetracaine group ingested fewer hydrocodone tablets (5.9) compared with the placebo group. This finding shows that short-term topical anesthetic use for acute complicated corneal abrasions could reduce or eliminate opioid prescriptions.

In accordance with this study and prior literature, we believe that emergency clinicians can safely prescribe

patients with uncomplicated corneal abrasions topical anesthetics for 24 hours as long as they are provided close ophthalmology follow-up and return precautions.

In conclusion, this study shows that short-term topical tetracaine is a safe and efficacious analgesic for acute, uncomplicated corneal abrasions, and is associated with less hydrocodone use compared with placebo.

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work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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