

An Observational Study to Determine Whether Routinely Sending Patients Home With a 24-Hour Supply of Topical Tetracaine From the Emergency Department for Simple Corneal Abrasion Pain Is Potentially Safe

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Study objective: To determine if the number of emergency department (ED) rechecks, persistent fluorescein uptake, ophthalmology referrals, or complications would be affected by the prescription of topical tetracaine for pain relief from simple corneal abrasions (SCAs).

Methods: This retrospective cohort study was conducted in an ED where policy change allowed physicians to use topical tetracaine hydrochloride 1% eye drops for 24 hours for pain treatment for patients with corneal abrasions. Outcomes were compared between patients who did or did not receive tetracaine (adjusting for the propensity for treatment).

Results: Of 1,576 initial ED presentations, 532 were SCAs, with 1,044 deemed nonsimple corneal abrasions (NSCAs). Tetracaine was dispensed at the initial visit for 303 SCA presentations (57%) and inappropriately for 141 NSCA presentations (14%). There were no serious complications or uncommon adverse events attributed to tetracaine for all SCAs and NSCAs combined (0/459; upper 95% confidence interval [CI] 0.80%). The relative risks (RRs) of ED recheck and fluorescein staining were increased overall among patients who received tetracaine (RR 1.67, 95% CI 1.25 to 2.23; and RR 1.65, 95% CI 1.07 to 2.53 for recheck and staining, respectively). However, the relative risks for only SCAs receiving tetracaine was 1.16 (95% CI 0.69 to 1.93) and 0.77 (95% CI 0.37 to 1.62), respectively. Referrals to ophthalmology were significantly decreased for all patients (SCAs and NSCAs) dispensed tetracaine (relative risk 0.33; 95% CI 0.19 to 0.59). The number of complications was too small to permit modeling.

Conclusion: There was no evidence that up to 24-hour topical tetracaine for the treatment of pain caused by SCA was unsafe; however, CIs were wide and some increased risks were observed for NSCAs. [Ann Emerg Med. 2017;■:1-12.]

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

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INTRODUCTION

Background

Pain from corneal abrasions caused by foreign bodies or trauma is a common complaint in the emergency department (ED). Traditional management has been to administer topical anesthetic drops such as tetracaine and remove the foreign body if it is still present. Patients can then be sent home with oral analgesia or topical nonsteroidal anti-inflammatory drops, as well as topical antibiotics.¹⁻³

Tetracaine, also known as amethocaine, is an ester-type anesthetic. Undiluted 1% tetracaine has a fast onset (10 to

20 seconds) and a short period of action (10 to 20 minutes) but has been reported to last up to 1 hour.^{1,4} Although effective in reducing pain, its continued use by the patient has been discouraged because of concerns over safety and is prohibited according to traditional teaching.^{5,6} Case reports of topical anesthetic abuse and misuse,⁷⁻³² coupled with animal studies,³³⁻³⁹ suggest that the use of topical tetracaine could lead to uncommon adverse events. Correction for these uncommon adverse events may include hospitalization, oral corticosteroids, contact lens bandages, and surgical procedures such as conjunctival flap, corneal transplantation, and penetrating keratoplasty.^{21,30}

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

Short-course topical anesthetic use for corneal abrasion pain is discouraged because of potential corneal toxicity.

What question this study addressed

Is limited (24-hour) treatment of simple corneal abrasion pain with topical tetracaine safe?

What this study adds to our knowledge

This single-center observational study of 1,980 patients with corneal abrasions found no serious complications among 459 instances of tetracaine use.

How this is relevant to clinical practice

Limited use of topical tetracaine for pain control of simple corneal abrasion may be acceptable, but large prospective studies are required to confirm safety.

evidence-based recommendations to be made. The potential clinical influence of these results could lead to better pain control for this common ED complaint at minimal cost and with a low risk of adverse outcomes.

Goals of This Investigation

We determined whether the routine use of a limited 24-hour supply of topical tetracaine for SCAs in an ED would be safe by comparing data of patients with corneal abrasions who did and did not receive tetracaine. Although the focus is on SCAs, understanding the potential effects on nonsimple corneal abrasions (NSCAs) is also important because inappropriate prescription is an inherent risk.

The primary hypothesis was that numbers of ED rechecks, persistent fluorescein uptake, ophthalmology clinic referrals, and complications would not differ for patients receiving topical tetracaine for short-term pain relief, in particular for those with SCAs.

MATERIALS AND METHODS**Study Design and Setting**

This retrospective cohort study took place at the ED of Southland Hospital, Invercargill, New Zealand. The hospital is a regional referral center servicing a population of approximately 93,300 over an area of 34,347 km². Emergency physicians at Southland Hospital gradually began to adopt the routine use of topical tetracaine for SCA in March 2014. The ED experiences an estimated 37,000 presentations a year and is the only hospital and ophthalmology clinic in the region, making it an ideal location for data collection and follow-up. In Southland, patients with corneal abrasions are treated in the ED and it is standard practice to recommend they return to the ED in 48 hours if they are not improving, sooner if symptoms worsen or at the discretion of the treating physician. Fluorescein staining at ED recheck is generally conducted to determine healing. Fluorescein staining was performed if symptoms were persistent; however, it was not conducted if there was a persistent foreign body or there were repeated attempts at foreign body removal in the ED on that visit because staining would be expected to show uptake. Follow-up in the ophthalmology clinic is reserved for patients with corneal abrasions that are not resolving normally or are complicated, or for other corneal diagnosis. Ophthalmology clinic referrals were made at the ED recheck if there were concerning features. There was no standard time frame for this referral, which was made on a case-by-case basis.

ED patients are treated by a mixture of junior physicians (interns), emergency physicians in training (residents),

In contrast, the literature defending the controlled use of a limited supply of topical anesthetics for simple corneal abrasions (SCAs) is increasing. Four studies have looked at the use of topical anesthetics after photorefractive keratectomy surgery.⁴⁰⁻⁴³ Applied to clean surgical wounds, they were shown to effectively treat pain and not delay wound healing. Subsequently, 3 ED studies⁴⁴⁻⁴⁶ looked at the treatment of pain caused by SCA. The results of the first 2 studies^{44,45} showed no serious complications and a reduction of pain. In 2014, a larger randomized controlled trial also supported the safety of topical tetracaine.⁴⁶

Two publications subsequently reviewed different combinations of these ED studies. Swaminathan et al⁴⁷ concluded that topical anesthetics are a safe and effective means of pain control in this patient population. However, Puls et al⁴⁸ concluded that because of a sparsity of data, the safety and effectiveness of this treatment is currently not supported by evidence. The most recent suggestion that thoughts on the topic are changing came in the 2015 edition of *Emergency Medicine Secrets*, stating that "...consensus is evolving regarding short-course therapy for uncomplicated corneal abrasions."⁵

Importance

Although highly effective in reducing pain, continued use of topical anesthetics has long been discouraged. Previous studies have suggested possible safety for short-term use; however, the studies have been small and there is a paucity of data. Larger and well-designed studies are needed to confirm or disprove these positions and allow

senior emergency physicians (non-ED trained), and ED-trained specialists (ED attending physicians). Physicians were educated about the proper use of tetracaine for SCAs and advised that NSCAs should not receive tetracaine.

This was an observational study designed to assess the outcomes and safety of routine tetracaine use. The use of tetracaine for SCA was not compulsory; some physicians adopted its use immediately, others remained cautious and adopted later, and a minority were still not convinced of its safety at the end of the study and never adopted the practice. Locum emergency physicians and some of the new junior physicians were not initially orientated about tetracaine use. This led to irregular adoption throughout the study period.

Ethics approval was given by the Human Ethics Committee (Health), University of Otago. All medications were stock items available in our ED.

Selection of Participants

Our physicians gradually began to adopt the use of tetracaine beginning in March 2014. Computer searches of the Hospital's Emergency Department Information System for all eye-related diagnoses identified 2,635 ED visits. Charts were reviewed from February 1, 2014, until October 31, 2015. A broad search was selected to ensure that data for any patient who might have received tetracaine for any possible diagnosis was captured. Researchers immediately excluded 363 charts because they were duplicate presentations or did not have any involvement of the eye. The remaining 2,272 charts were reviewed and an additional 292 charts were excluded because the injury or illness did not involve the cornea. This left 1,980 charts included in the study. This comprised 1,576 initial ED presentations potentially followed by one or more subsequent ED rechecks involving 1,402 distinct patients. To be able to show the upper limit of uncommon adverse events related to tetracaine with the upper limit from an exact binomial 95% confidence interval (CI) no greater than 1.30% (ie, a 95% CI of 0.00% to 1.30%) would require at least 300 patients receiving tetracaine with no events observed in this group.

Interventions

Our ED's standard treatment for corneal abrasions consists of chloramphenicol eye ointment and a prescription for 2 paracetamol 500-mg tablets every 4 hours as needed. Tetracaine-treated patients were sent home with 1.5 mL of preservative-free undiluted 1% tetracaine hydrochloride in addition to the standard treatment. Tetracaine was supplied in a premade take-home pack

consisting of 3 plastic 0.5-mL commercially available vials, or approximately 50 drops. Patients were asked to place tetracaine in their eye as often as every 30 minutes while awake for up to 24 hours. Although there were no written instructions given for its use, physicians instructed patients to avoid rubbing their eyes after use. Aftercare instructions were given asking patients to return if they had any concerns or worsening symptoms, or were experiencing persistent symptoms after 48 hours.

Methods of Measurement

An SCA was defined as a corneal abrasion (fluorescein uptake on the cornea) that was not large (size subjectively determined by the physician), penetrating, or lacerating. It should have occurred within the past 2 days and be due to a simple traumatic cause, not from chemicals, contact lens use, thermal burns (other than ultraviolet flash burns), contaminated wounds, or infection. It should not have a retained foreign body such as a rust ring after removal in the ED, nor be in a patient younger than 15 years, and should not require the immediate attention of an ophthalmologist. Patients meeting these criteria were determined to be at low risk according to previous studies.⁴⁴⁻⁴⁶ Presentations that did not meet these criteria were classified as NSCAs by the chart reviewers.

To better delineate the different complications for the purpose of this study, we defined a minor or temporary complication to be when a patient required 2 to 3 ophthalmology clinic visits (initial visit and 1 to 2 follow-ups) to resolve either their symptoms or their condition, or to remove retained rust rings or retained foreign bodies. We defined serious or permanent complications to be when a patient required 4 or more ophthalmology clinic visits, hospitalization, or corrective procedures or underwent any permanent condition or alteration in vision. Uncommon adverse events specific to tetracaine use (Figure 1) have been reported in a number of case reports that examined topical anesthetic abuse and misuse.⁷⁻³² The terms *minor or temporary complication, serious or permanent complication, and uncommon adverse events* were used in an attempt to distinguish between complications that may be expected with routine treatment and healing versus uncommon adverse events that have been implicated with the use of tetracaine.

Chart reviewers, who were not blinded to the study hypothesis, underwent a training session with the principal investigator (N.W.) before performing data extraction. A standard data extraction sheet was used to increase reliability, and data that were specifically present in the chart were allowed to be included.⁴⁹ The only exception was when information in regard to the time that the injury

Prolonged healing
Persistent corneal epithelial defect
Corneal perforation
Ulceration
Neurotropic ulcer
Surface keratopathy
Ring keratopathy
Corneal stromal infiltration
Toxic keratitis
<i>Candida</i> keratitis
Bacterial keratitis
Uveitis
Hypopyon
Hyphema
Corneal infiltrates

Figure 1. Reported tetracaine-specific uncommon adverse events.

occurred was missing. If it was obvious from the chart it had occurred within the previous 2 days, it was coded this way. Details of the timing and mechanism of injury, symptoms, and physical examination findings were collected. The principal investigator (N.W.) reviewed anomalous charts. One dedicated study investigator (I.D.) entered all the data into a spreadsheet and scrutinized all of the data extraction sheets, as well as the designation of SCA versus NSCA. Any complicated or anomalous data extraction sheets were brought to the attention of the principal investigator (N.W.) for final interpretation with other study investigators. Periodic meetings and discussion were held between investigators.⁴⁹ Any patient receiving tetracaine at any stage of his or her treatment, whether it was the first, second, third, or subsequent visit, was considered part of the tetracaine group, but statistical analyses were based on tetracaine dispensed at the initial presentation.

The classification of SCA versus NCSA was determined by the data abstractor according to the rules of classification and on the information in the chart. All ED recheck patients had their charts reviewed. All patients who received tetracaine for any diagnosis and later went to the ophthalmology clinic had their notes reviewed by the principal investigator (N.W.) and the data entry investigator

(I.D.). Patients in the SCA tetracaine group (SCA-TET), SCA standard treatment group (SCA-ST), and NSCA tetracaine group (NSCA-TET) had complete records available and ophthalmology clinic notes were reviewed. Ophthalmology clinic referral information was available for 82.3% of the NSCA standard treatment group.

Interrater reliability was measured by selecting a random sample of 5% of the charts. A total of 100 charts were assessed by a second reviewer for the key outcomes of classification of SCA versus NSCA, determining whether the patient was sent home with tetracaine, and determining whether the patient was referred to the ophthalmology clinic. κ Statistics for these 3 binary measures were SCA 0.63 (82% agreement), tetracaine 0.94 (97% agreement), and referral 0.96 (99% agreement), all of which are greater than 0.60 and so considered here as acceptable.⁵⁰

Outcome Measures

Outcome measures were ED rechecks, persistent fluorescein uptake, ophthalmology clinic referrals, or complications. ED rechecks were chosen as a surrogate marker for prolonged symptoms or delayed healing. Persistent fluorescein was also chosen as a marker for delayed healing. Ophthalmology clinic referrals were chosen to look for potential minor or temporary complications, major or permanent complications, and uncommon adverse events.

Primary Data Analysis

All data (February 2014 to October 2015) were used to examine the effects of tetracaine being dispensed at the initial presentation at the ED for a corneal abrasion event. The outcomes of interest were a recheck taking place at the ED, positive fluorescein staining at a subsequent recheck (excluding patients with retained or unexpected rust rings at the time), and referral to ophthalmology. Sensitivity analyses were performed limiting the date range to initial presentations from April 2014 onward (when the change in policy was initiated) and from June 2014 onward (when the change in policy had been fully implemented).

Propensity scores were calculated with a logistic regression model to estimate the probability of receiving tetracaine at the initial presentation for each event. Variables used to calculate this probability are shown in Figure 2. Six treating physicians (with between 2 and 22 SCAs each, 36 in total; and a further 8 to 24 NSCAs each, 83 in total) never dispensed tetracaine, so probabilities associated with them could not be directly estimated from this logistic regression model. Their propensities were set to zero, reflecting their consistent nonuse of tetracaine. All variables needed for the propensity score modeling were

Time of the initial presentation (measured in days from the start of the period with nonlinearities assessed with likelihood ratio tests to determine whether the successive addition of quadratic, cubic, and quartic terms improved model fit)
Whether the abrasion was considered simple at initial presentation (yes/no)
ED shift (midnight to before 8 AM, 8 AM to before 5 PM, 5 PM to before midnight)
Patient age (using categories of <5, 5–14, 15–24, etc, and ≥85 y)
Patient sex (male, female)
Injury mechanism (involving a foreign body, involving direct trauma, involving both, and involving neither)
Pain (yes/no)
Blurry vision (yes/no)
Change in vision (yes/no)
Treating physician (where all physicians with fewer than 10 initial presentations were combined into a single “other” category)
Consulting physician (where, similarly, all physicians with fewer than 10 initial presentations were combined into a single “other” category)

Figure 2. Variables used to calculate the probability for the propensity scores.

available for all patients. Deciles of propensity scores were then calculated, and the associated categories of propensity scores were included as a 10-level categorical variable in mixed-effects (to accommodate some patients presenting for multiple events) Poisson regression models, allowing estimation of relative risks and associated 95% CIs for each of the 3 outcomes of interest. Interactions between abrasion type (SCA and NSCA) and receiving tetracaine at the initial presentation were examined to identify and model effects of tetracaine prescription for each type of corneal abrasion.

Exact binomial CIs were constructed for uncommon adverse events for both appropriate use of tetracaine (ie, patients with SCA) and all patients with corneal abrasions. Data were analyzed with Stata (version 14.2; StataCorp, College Station, TX) and R (version 3.3.2; R Core Team, Vienna, Austria), and 2-sided $P<.05$ was considered statistically significant in all cases.

RESULTS

Characteristics of Study Subjects

Table 1 shows baseline demographics and clinical characteristics of all patients. **Figure 3** demonstrates the flow of patients through the study.

The adoption of tetracaine use for SCA increased markedly during May and June 2014 and appeared to achieve a plateau from July 2014 onward. An average of 59.5% of SCA patients received tetracaine between July 2014 and October 2015, as shown in **Figure 4**.

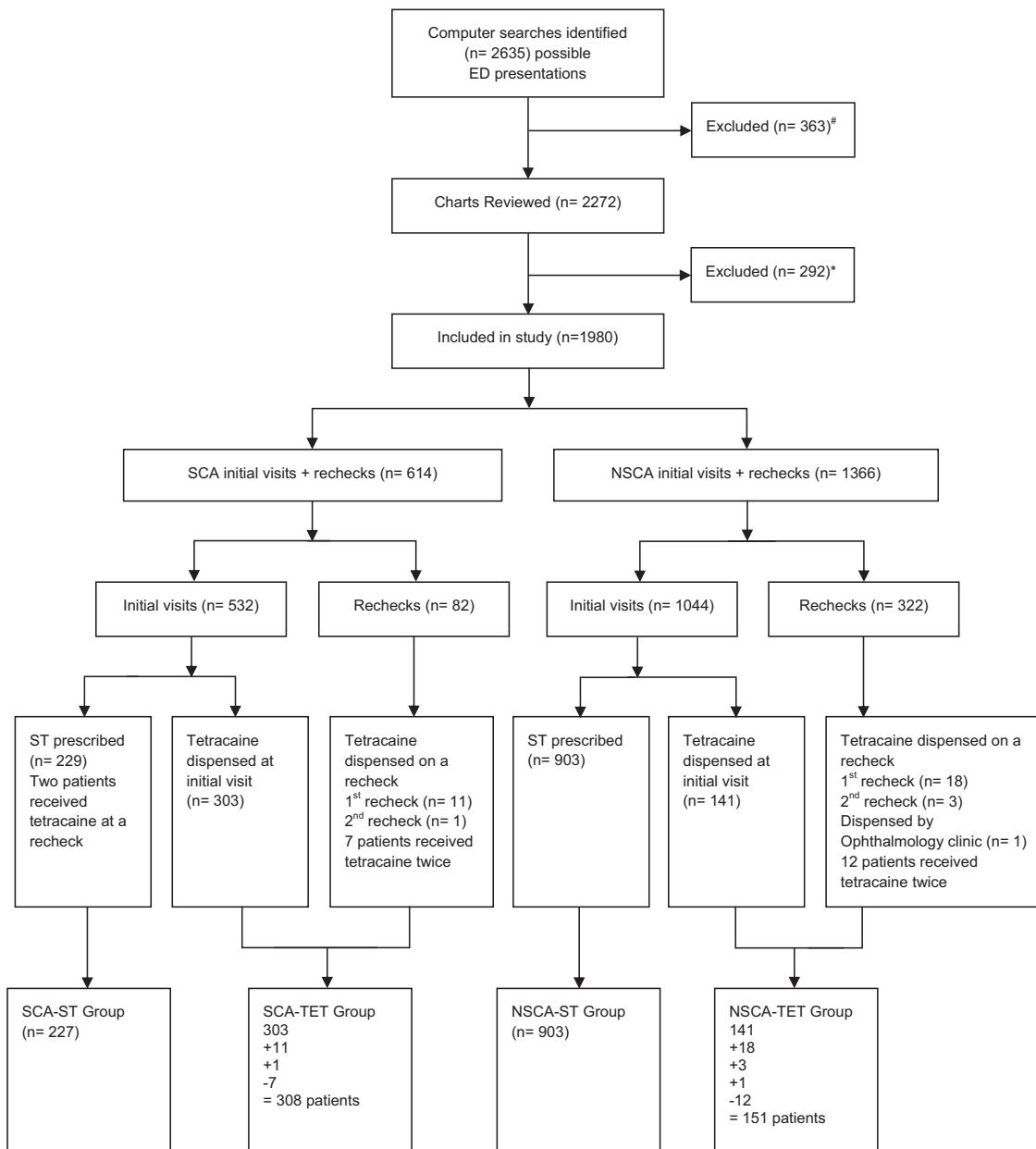
The SCA group comprised 532 initial ED presentations (**Figure 3**). Comparing SCAs that did or did not receive tetracaine on initial presentation, of the 303 patients who received tetracaine, 46 returned for one or more rechecks. Of the 229 patients receiving standard treatment, 26 returned for one or more rechecks. There were 6 unexpected retained rust rings among the patients who received tetracaine on their first visit and 2 in the standard treatment group. After removal of the unexpected rust rings, the fraction of patients requiring a subsequent ED recheck was 40 of 297 SCA-TET (13.5%) and 24 of 229 SCA-ST (10.5%).

Of the 72 presentations that resulted in the patient's returning for a recheck in the SCA group, 63 of 72 patients underwent fluorescein staining. After removal of 6 patients with unexpected rust rings that were stained, there were 34 patients with positive fluorescein uptake. The group that received tetracaine on their initial visit had fluorescein

Table 1. Baseline demographics and clinical characteristics.

Demographics	1,402 Distinct Patients
Age, mean (SD, minimum–maximum) over all initial presentations, y	38.1 (19.4, 0–91)
Sex, No. (%)	
Male	1,006 (71.8)
Female	396 (28.2)
Characteristics	1,576 Initial Presentations
Primary mechanism of injury, No. (%)	
Metallic FB	370 (23.5)
Unknown FB	202 (12.8)
Wood FB	62 (3.9)
Other FB	84 (5.3)
Dirt/dust/gravel FB	38 (2.4)
Glass FB	4 (0.3)
Direct trauma, branch/stick	36 (2.3)
Direct trauma, finger/fingernail	16 (1.0)
Direct trauma, other	95 (6.0)
Direct trauma, unknown	12 (0.8)
Welders flash/UV keratitis	46 (2.9)
Other/unknown/not described	611 (38.8)
Classification of injury, No. (%)	
SCA	532 (33.8)
NSCA	1,044 (66.2)

FB, Foreign body; UV, ultra violet.



* 297 charts excluded because they were duplicate presentations or did not have any involvement of the eye.

* 292 charts excluded because the injury or illness did not involve the cornea.

Figure 3. Patient flow through the study.

uptake 47.1% of the time (16/34), whereas the standard treatment patients had fluorescein uptake 52.9% of the time (18/34).

One patient in the SCA-TET and 4 in the SCA-ST group had ophthalmology clinic follow-up visits. A complete list of all SCA ophthalmology clinic outcomes is shown in Table 2. No rust rings were identified in the SCA-TET group and one was identified in the SCA-ST group. The fraction of patients needing ophthalmology clinic follow-up was 1 of 308 for the SCA-TET group

(0.3%) versus 4 of 227 for the SCA-ST group (1.8%). Patient A from the SCA-TET group experienced a mild corneal haze, in which a rust ring removal was attempted first by the general practitioner in the office and was later completed in the ED. Four patients in the SCA-ST group received a diagnosis of a persistent rust ring (patient B), scleritis (patient C), a recurrent corneal erosion (patient D), and a corneal erosion (patient E).

The NSCA standard treatment group contained 903 initial ED presentations. The NSCA-TET group was made

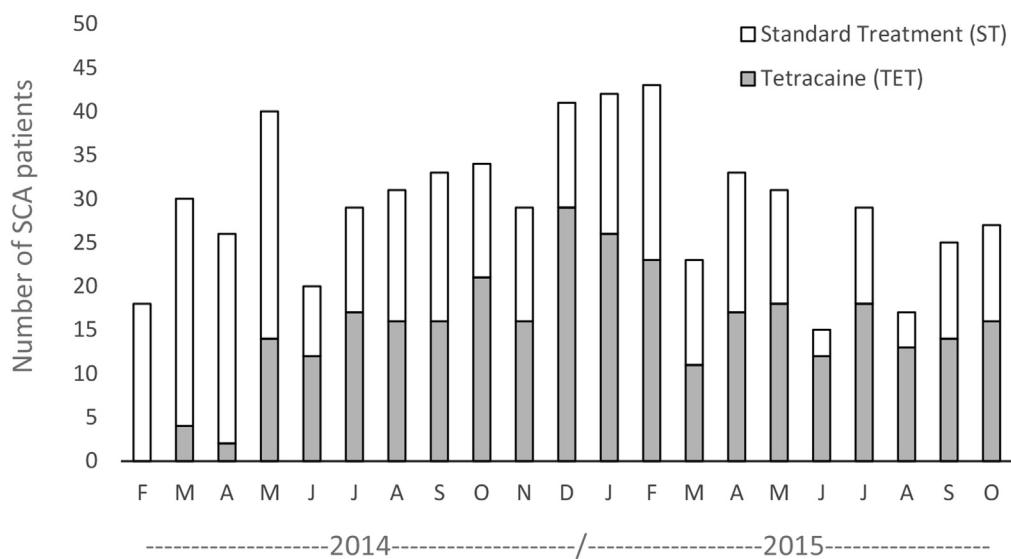


Figure 4. Adoption of tetracaine use for SCA, February 2014 to October 2015.

up of 151 patients given tetracaine a total of 162 times (141 on the initial ED presentation, 18 on the first recheck, and 3 on the second recheck; 1 patient received tetracaine from the ophthalmology clinic before presenting to the ED). Twelve patients received tetracaine twice. There were 74 patients in this group who returned for one or more rechecks. Of the 74 presentations that resulted in the patient's returning for a recheck in the NSCA-TET group, 43 of 74 patients underwent fluorescein staining. After removal of 12 patients with rust rings that were stained, there were 19 patients with positive fluorescein uptake.

Of the 151 total patients who received tetracaine (NSCA-TET), 17 went to the ophthalmology clinic. A complete list of the diagnoses, ophthalmology clinic treatment, and type of complications is shown in [Table 3](#). Five of these patients (patients 1 to 5) received a diagnosis of retained rust rings, and a further 5 (patients 6 to 10) received a diagnosis of corneal abrasions, large corneal abrasions, erosions, or chemical erosions. One patient

received a diagnosis of herpes keratitis (patient 11), 2 patients received a diagnosis of recurrent corneal erosions (patients 12 and 13), and 1 received a diagnosis of severe anterior uveitis (patient 14). Patient 15 was sent home with tetracaine on the second ED recheck and initially received a misdiagnosis of conjunctivitis, later receiving a diagnosis of episcleritis. A patient being treated with Avastin (bevacizumab) received take-home tetracaine from an ophthalmologist the evening before the ED presentation (patient 16). This patient received additional tetracaine in the ED on the advice of the consulting ophthalmologist and required an ophthalmology clinic follow-up related to pain from the injection and experienced no complications. Patient 17 had traumatic mydriasis and experienced a minor or temporary complication of pupil dilation and temporary vision changes.

We did not intend for patients with retained rust rings who left the ED to receive tetracaine; however, this occurred. An unplanned post hoc comparison was made on 91 patients in the NSCA group who were identified as

Table 2. SCA ophthalmology clinic outcomes.

Patient	Initial ED Diagnosis	Final Ophthalmology Clinic Diagnosis	Tetracaine Given	No. of ED Visits	No. of Ophthalmology Clinic Visits	Minor/Temporary Complication	Reason	Serious/Permanent Complication	Reason
A	Corneal foreign body	Corneal haze	Yes	1	1	Yes	Corneal haze	No	
B	Rust ring	Rust ring	No	2	1	No		No	
C	Corneal abrasion	Scleritis	No	2	1	No		No	
D	Corneal abrasion	Recurrent corneal erosion	No	2	3	Yes	Recurrent corneal erosion, 3 visits	Yes	Ongoing condition
E	Corneal abrasion	Corneal erosion	No	2	2	Yes	Corneal erosion, 2 visits	No	

Table 3. Ophthalmology clinic outcomes for NSCA-TET patients.

Patient	ED Diagnosis	Final Diagnosis	Ophthalmology Clinic Treatment	No. of ED Visits	No. of Ophthalmology Clinic Visits	Minor/Temporary Complication	Reason	Serious/Permanent Complications	Reason
1	Rust ring	Rust ring	Rust ring removal, antibiotics	2	2	Yes	Rust ring, 2-3 visits	No	
2	Rust ring	Rust ring	None	1	0	No	Unknown, patient had no symptoms and declined ophthalmology clinic referral	No	
3	Rust ring	Rust ring	Antibiotics, attempted removal	3	2	Yes	Rust ring, 2-3 visits	No	
4	Rust ring	Rust ring	Removal	3	1	No		No	
5	Rust ring	Rust ring	Repeated burring, antibiotics	2	4	Yes	Persistent symptoms	Yes	Ophthalmology clinic unable to fully remove FB, repeated burring, mild corneal staining with scar formation at FB site, 4 visits
6	Corneal abrasion, rust ring	Corneal abrasion	Antibiotics, eye patching	4	4	Yes	Small corneal scar, repeated burring	Yes	Small corneal scar, 4 visits
7	Large corneal abrasion	Corneal abrasion/erosion	Antibiotics	3	2	Yes	Persistent symptoms, altered vision, 2-3 visits	No	
8	Large corneal abrasion	Corneal erosion	Antibiotics	3	2	Yes	Persistent symptoms, 2-3 visits	No	
9	Large corneal abrasion	Large corneal abrasion	Antibiotics, eye patching	3	2	Yes	Diminished vision, slow healing, 2-3 visits	No	
10	Chemical corneal erosion	Chemical corneal erosion	Antibiotics	1	3	Yes	Persistent symptoms, 2-3 visits	No	
11	Dendritic ulcer	Herpes keratitis	Steroid drops, antibiotics, antivirals	2	6	Yes	Diminished vision, corneal haze, corneal scars	Yes	Diminished vision, corneal haze, corneal scars, ≥4 visits
12	Large corneal abrasion	Recurrent corneal erosion	Antibiotics	4	6	Yes	Developed corneal infiltrates	Yes	Corneal scarring, ≥4 visits
13	Corneal ulcer	Recurrent corneal erosion	Antibiotics	1	2	Yes	Persistent symptoms	Yes	Recurrent corneal erosion, ≥4 visits
14	Conjunctivitis, possible corneal abrasion	Severe anterior uveitis	Tests for autoimmune disease, steroid drops	2	4	Yes	Cells in anterior chamber, developed posterior synechia, diminished vision	Yes	Cells in anterior chamber, developed posterior synechia, diminished vision, 4 visits
15	Conjunctivitis	Episcleritis	Tests for autoimmune disease, anti-inflammatory medications, steroid eye drops	3	3	Yes	Pain, 2-3 visits	No	
16	Injection pain	Avastin (bevacizumab) injection pain	Ophthalmology clinic recommended ED to prescribe tetracaine, oral pain medications	1	1	No		No	
17	Traumatic mydriasis, corneal abrasion	Traumatic mydriasis	Steroid drops	2	2	Yes	Pupil dilation, abnormal vision, 2-3 visits	No	

having a retained rust ring at their first ED recheck. These patients required repeated ED visits to remove the retained rust rings. Of the 91 patients, 39 received tetracaine on their initial visit. Only one patient from each of the tetracaine and standard treatment groups required an ophthalmology clinic follow-up to remove the rust ring. There were no complications identified that were directly related to tetracaine use with retained rust rings.

Fifteen patients who were younger than 15 years received tetracaine; of these, 6 returned to the ED for a recheck. None of these patients appeared to have any complications or required ophthalmology clinic follow-up.

The binomial exact 95% CI for complications occurring in the SCA-TET group ($n=308$) has an upper limit of 1.19% for these types of events. Among the 151 NSCA-TET patients, there were no events resulting in an upper limit of 2.41%. In combining both groups, there were no uncommon adverse events for all 459 patient presentations when tetracaine was dispensed (including inappropriately); the exact 95% CI upper limit was 0.80%.

Most of the a priori-selected propensity score variables were significantly associated with tetracaine's being dispensed (from simple logistic regression models: SCA, the day with quadratic and cubic terms included according to results from likelihood ratio tests, age category, sex, injury mechanism, pain, treating physician, and consulting physician), although shift, change in vision, and blurry vision were not. All a priori-selected variables were included in the calculation of propensity scores. The relative risk for ED recheck for all patients was 1.67 (95% CI 1.25 to 2.23), but for only patients with SCA, the relative risk was 1.16 (95% CI 0.69 to 1.93). The relative risk for fluorescein uptake was 1.65 (95% CI 1.07 to 2.53) and 0.77 (95% CI 0.37 to 1.62) for all patients and SCA patients, respectively. Table 4 summarizes the result for all modeled outcomes for all patients and those in either the SCA or NSCA group, as described below.

From mixed-effects Poisson regression models including the propensity score classified with deciles, we estimated the relative risk for a recheck after initial dispensing of

tetracaine to be significantly elevated overall. There was no evidence that this effect varied between SCA and NSCA, with a nonsignificant reduction in risk in the SCA group, but statistically significant evidence of increased risk of rechecks after prescription of tetracaine was observed only for the NSCA.

The relative risk of fluorescein uptake at a subsequent recheck was significantly elevated overall, but there was evidence that the effects differed between SCA and NSCA, with a significant reduction in risk for the SCA group and with evidence of increased risk of staining in the NSCA group but not in the SCA group.

The relative risk of referral to ophthalmology was overall significantly decreased after initial prescription of tetracaine, being approximately one third of the risk otherwise. There was no evidence of an interaction, and the point estimate was close to 1.00 in this case, but the reduced risk was noted only in the NSCA group and not in the SCA group.

The number of complications was too small to permit modeling. The associations were not meaningfully changed by excluding initial events before April 2014 or excluding initial events before June 2014 (results not shown).

LIMITATIONS

The researchers were not blinded to the study hypothesis and could have biased the data collection. This risk of bias was minimized by a standard data extraction sheet and also by having a second researcher scrutinizing the data while entering it into the computer. All anomalous answers were subject to inspection. Physicians were not aware that a subsequent chart review was planned, and there is no reason to suspect that their use of tetracaine was based on anything other than their view, at the time, of the best treatment for each patient.

We were limited by the information in the chart, relying on the description by the physician of the corneal abrasion and documentation in regard to treatment. Patients were sent home with instructions to receive paracetamol and tetracaine, but whether they received their medications as directed was not specifically asked, and even if this question

Table 4. Results of Poisson regression model.

Outcome Measure	Combined, RR (95% CI)	SCA, RR (95% CI)	NSCA, RR (95% CI)	Interaction for the Effect of Being Dispensed Tetracaine, RR (95% CI)
Recheck	1.67 (1.25–2.23)	1.16 (0.69–1.93)	1.94 (1.41–2.67)	0.60 (0.33–1.06)
Fluorescein uptake	1.65 (1.07–2.53)	0.77 (0.37–1.62)	2.19 (1.38–3.48)	0.35 (0.15–0.82)
Referral to ophthalmology	0.33 (0.19–0.59)	0.34 (0.06–1.95)	0.35 (0.20–0.64)	0.94 (0.15–5.95)
Complications	The number of complications was too small to permit modeling.			

RR, Relative risk.

had been asked, it would be impractical to confirm. However, the study's goals were pragmatic and centered around the incidence of events under actual conditions after dispensing of tetracaine rather than under laboratory conditions. We were able to access only patients who returned for rechecks, and it is possible that some patients developed scars or defects in their vision but did not return to either the ED or the ophthalmology clinic.

A limitation of the propensity score modeling is that the actual size of the abrasion was not available for any patients and the time since injury was not available for NSCA patients, and so these potential confounders could not be included in the propensity score model. The number of events in which tetracaine was dispensed within the cohort did not permit further investigation of interactions between predictors in this model. The 95% CIs for relative risks were generally wide in the SCA group, and so it is possible that clinically important effects were not detected in this study, although there was a lack of evidence of any effects in this group.

Standard ED equipment was limited to fluorescein staining with slit lamp examination. We did not use sophisticated optical devices to define the corneal injuries or to detect healing abnormalities on a microscopic level. In retrospect, our measure of ED rechecks was too imprecise, and we could not reliably determine from the notes whether rechecks were planned or unexpected. Patients returning for unexpected rechecks were experiencing symptoms, whereas those with planned rechecks may or may not have had symptoms. It is possible that recheck numbers for the tetracaine groups were higher because of overcautiousness in planned rechecks among new physicians adopting the practice, which would inflate recheck numbers in the tetracaine group.

DISCUSSION

Consistent with our ED's earlier research, this current study also found no important difference in the number of ED rechecks or ophthalmology clinic referrals, or persistence of fluorescein uptake between the tetracaine group and the standard treatment group for SCA, which is similar to the findings of previous smaller studies.^{44,45} However, increased risks of ED rechecks and persistence of fluorescein uptake were observed among NSCA patients who were inappropriately dispensed tetracaine. Referrals to an ophthalmology clinic were, however, lower among NSCA patients who received tetracaine.⁴⁶

Similar to our previous study,⁴⁶ the complication rate was exceedingly small and tetracaine use did not appear to cause any serious long-term complications even when it was

inappropriate. In this study, patients were mistakenly given tetracaine for herpes keratitis, iritis, recurrent corneal erosions, large corneal abrasions, chemical abrasions, episcleritis, and persistent corneal abrasions. Complications and ophthalmology clinic follow-up visits appeared to be related to the underlying condition rather than tetracaine use.

Tetracaine was inappropriately dispensed mostly in instances of persistent rust rings, injury older than 2 days, undocumented time of injury, no clear history or trauma or fluorescein uptake, younger than 15 years, or possibly contaminated foreign bodies. We have endeavored to improve our appropriate prescribing of tetracaine by the continued education of our physicians and the development of an information sheet for patients sent home with tetracaine. We expect that the use of tetracaine will continue to be a routine and safe practice in our ED.

We believe this to be one of the largest studies of its type to date. The results of this study are consistent with those of previous smaller studies and the larger numbers provide more precise estimates, although CIs for the effects with SCA still included clinically relevant effects.

This study used full-strength tetracaine rather than the dilute concentrations used in previous studies. Future studies could explore the possibility of using either different types of topical anesthetics or a duration of 36 or 48 hours. In this study, injuries older than 2 days were chosen to be unsafe, but it may be that longer time frames are safe. Retained rust rings were a contraindication to giving tetracaine; however, it appears that this may not be evidence based.

All analgesics prescribed to patients sent home from the ED have unique benefit-risk profiles. Our study, in conjunction with previous work establishing good pain relief, suggests a favorable profile for this limited topical treatment. The current investigation precludes a quantitative comparison of the benefit-risk profiles of topical tetracaine compared with acetaminophen, nonsteroidal anti-inflammatory drugs, or opioids. Qualitatively, however, it appears unlikely that topical tetracaine has a worse adverse event rate than that reported for these alternative agents. Much larger studies would be required to confirm superiority of topical tetracaine.

We found no evidence that topical tetracaine when used in a limited supply for 24 hours for SCAs is not a safe and effective means of controlling pain for SCAs. The conventional practice in regard to avoiding dispensing any topical anesthetic is not based on clinical studies but is founded on small case reports and animal studies with prolonged or uncontrolled use. Multiple clinical studies

have now found no evidence that controlled and limited use is unsafe, and this should inform new evidence-based guidelines. The investigators do not advocate an unlimited supply or dispensing to conditions other than SCAs. The lack of evidence for harms resulting from this practice may be a result of the limited supply given. We believe a short-term supply of tetracaine should become routine practice in the ED to treat this painful condition, although this recommendation would change should evidence of adverse outcomes be found through further investigation. Robust procedures are required to ensure it is not inappropriately prescribed because there was evidence of adverse outcome measures for NSCAs in terms of ED rechecks and persistent fluorescein uptake.

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Author contributions: NW and ID conceived and designed the study, obtained ethical approval for the research, supervised the conduct of the study and data collection, and drafted the article. NW, BW, ID, SM, GG, and JM performed data collection. ID managed the data, including quality control. AG provided statistical advice on study design and analyzed the data in consultation with NW and ID. All authors contributed substantially to article revision. NW takes responsibility for the paper as a whole.

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