

ORIGINAL CONTRIBUTION

Topical Tetracaine Used for 24 Hours Is Safe and Rated Highly Effective by Patients for the Treatment of Pain Caused by Corneal Abrasions: A Double-blind, Randomized Clinical Trial

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Abstract

Objectives: The objective of this study was to test the hypothesis that topical tetracaine would be safe to use for 24 hours and would not affect corneal healing, that patients would experience more pain relief, and that patients would perceive tetracaine to be more effective than saline eye drops for the treatment of pain caused by corneal abrasions.

Methods: The study was a 12-month, prospective, double-blind, randomized trial of tetracaine versus saline set in the emergency department (ED) of a regional tertiary care teaching hospital. A total of 116 patients presenting with uncomplicated corneal abrasions were included in this study. The intervention was either undiluted, preservative-free, topical tetracaine hydrochloride 1% or saline, applied up to every 30 minutes while awake for 24 hours. Main safety outcome measures were repeat ED examinations at 48 hours with fluorescein staining and slit-lamp examination, 1-week and 1-month telephone interviews with additional examinations as needed, and monitoring of charts for complications. Secondary outcome measures were 100-mm visual analogue scale (VAS) pain scores recorded every 2 hours while awake for 48 hours and patient-perceived overall effectiveness using a numeric rating scale (NRS) of 0 to 10 obtained during telephone interviews.

Results: At least one follow-up encounter was completed on each of the 116 patients. No complications specifically attributed to topical anesthetic use occurred in the 59 patients in the tetracaine group, and the binomial probability confidence interval (CI) of this occurring is 0 to 6.1. There was no significant difference in corneal healing as measured by the percentage of patients with persistent fluorescein uptake at 48 hours between the two groups (23.9% vs. 21.3%, difference = 2.6%, 95% CI = -14% to 20%, $p = 0.761$) or persistent symptoms at 48 hours (21.7% vs. 21.3%, difference = 0.4%, 95% CI = -16% to 17%, $p = 0.957$). There was no clinical difference in VAS pain scores between the groups. Patients in the tetracaine group rated the study drugs' overall effectiveness significantly higher on the NRS (7.7 vs. 3.9) compared to patients in the saline group (difference = 3.9, 95% CI = 2.4 to 5.3, $p < 0.0005$).

Conclusions: Topical tetracaine used for 24 hours is safe, and while there was no significant difference in patient VAS pain ratings over time, patient surveys on overall effectiveness showed that patients perceived tetracaine to be significantly more effective than saline.

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Pain from corneal abrasions caused by foreign bodies or trauma is a common complaint.^{1,2} Our hospital's local practice is to instill topical anesthetic drops, remove the foreign body if still present, and then treat the corneal abrasion with topical antibiotics and oral analgesia.

Tetracaine, also known as amethocaine, is an ester-type anesthetic with a fast onset of action (10 to 20 seconds) and a short duration of action (10 to 15 minutes). Although highly effective in reducing the pain, continued use of topical anesthetics has long been discouraged because of case reports and animal studies showing complications from long-term use.³⁻¹² Challenges to the traditional teachings about continued use of topical anesthetics have come from eye surgeons who have been studying their safety and efficacy for a short supervised duration after photorefractive keratectomy (PRK) surgery. Two clinical trials involving PRK surgery showed no delayed healing from the use of topical anesthetics for postoperative pain.^{3,4} Whether these studies of surgically clean wounds could be applied to corneal abrasions in general was questioned by two small clinical trials carried out on patients presenting to hospital emergency departments (EDs) with corneal abrasions. These studies showed similar efficacy and safety, but low numbers resulted in them being underpowered to prove a statistical difference.^{5,6}

We conducted a randomized double-blind trial to test the hypothesis that topical tetracaine would be safe to use for 24 hours and would not affect corneal healing and that patients would experience more pain relief and would perceive tetracaine to be more effective than saline eye drops for the treatment of pain caused by corneal abrasions.

METHODS

Study Design

This was a prospective, randomized, double-blind trial of a convenience sample of patients with corneal abrasions or foreign bodies. All participants gave written informed consent before participation. There was no payment or reimbursement of expenses for participating in this study. The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12611000448943), and ethics approval was given by the New Zealand Health and Disability Ethics Committee, Upper South A Regional Ethics Committee (URA/11/05/011). There was no funding for the study and all medications were stock items available in our ED. There was no sponsorship or involvement with the drug manufacturer.

Study Setting and Population

The research ran from November 1, 2011, to October 31, 2012. The study took place at the ED of Southland Hospital, Invercargill, New Zealand. The hospital is a regional referral center servicing a population of approximately 94,900 over an area of 34,347 km². The ED sees an estimated 35,000 presentations a year and is the only hospital and ophthalmologic department in the region, making it an ideal location for data collection and follow-up. In Invercargill, it is common for patients

with corneal abrasions to present to the ED for treatment and it is standard practice to recommend that they return in 48 hours for a recheck. Ophthalmologic clinic visits are reserved for complicated cases and not for routine follow-up.

Inclusion criteria included any simple uncomplicated corneal abrasion from mechanical trauma or keratitis from ultraviolet light or from removal of foreign body by the physician. Patients who were at a high risk of infection or complication were specifically excluded by the criteria outlined in Table 1.

Study Protocol

Patients presenting to the ED with corneal abrasions or corneal foreign bodies were provided with an information sheet outlining the research and were asked to voluntarily participate. Patient enrollment into the study could occur at any time during the day or night, 7 days a week, and was dictated in part by staffing levels and demands on the department at the time. Patients were enrolled into the study by junior doctors (post-medical school 2 to 3 years) and senior doctors.

Numbered sealed envelopes were issued in sequential order by the physician enrolling the patient in the study. The contents of each envelope were randomized by the hospital's medical research officer who was not involved in the care of the patients. The randomization plan was unknown to the physicians enrolling patients. The principal clinical investigator was blinded to the randomization plan until all patients enrolled in the study had been assessed and follow-up interviews were completed. The randomization plan was generated using block randomization with random block sizes of six, eight, and 10 from a Web site (www.randomization.com).

Each study packet contained study instructions, a letter identifying the patient as a participant, a pain questionnaire, 500-mg paracetamol tablets, and either unlabeled saline or tetracaine (randomization ratio 1:1).

Table 1
Patients Were Excluded From the Study if They:

- Presented more than 36 hours after their initial injury
- Were under the age of 18 years*
- Had had previous eye surgery or cataracts
- Wear contact lenses or if their injury was caused from contact lens wear
- Had injured both eyes
- Were deaf
- Were unable to give informed consent
- Were suffering from infectious or chemical conjunctivitis
- Had a grossly contaminated foreign body in their eye
- Were suffering from an ocular infection
- Currently had herpes keratitis
- Were allergic to tetracaine or similar medication classes
- Had an injury requiring urgent ophthalmologic evaluation (e.g. penetrating eye injuries, large or complicated corneal abrasions, or injuries causing a significant disruption of vision)
- Were unable to attend follow up in 48 hours

*One 17-year-old patient enrolled with parental consent.

Tetracaine was supplied in three plastic prefilled, commercially available vials, each containing 0.5 mL of preservative-free, undiluted 1% tetracaine hydrochloride (a total of 1.5 mL or approximately 50 drops). Saline was supplied in a 5-mL single-use plastic bullet. Although a different size, the medications were packaged inside the questionnaire sheets, which were concealed inside a white envelope to disguise their identity. The packet was given to the patient with instructions to open it when he or she arrived home. Patients were asked to place the study medication in the affected eye as often as every 30 minutes while awake for the first 24 hours and to take two 500-mg paracetamol tablets at 08:00 hours, 12:00 hours, 16:00 hours, and 20:00 hours. All patients were additionally sent home with preservative-free 1% chloramphenicol antibiotic eye ointment as part of the standard treatment at Southland Hospital for corneal abrasions.

Patients were asked to record pain score measurements on a 100-mm visual analogue scale (VAS) every 30 minutes for the first 2 hours after leaving the ED and then every 2 hours for the next 48 hours while awake. They were also asked to indicate when their last dose of paracetamol had been taken.

Patients were reassessed at 48 hours by a senior doctor in the ED; physicians were asked to identify any complications, abnormalities, or patient complaints. Repeat slit-lamp examinations, fluorescein staining, and visual acuity were documented. Patients were contacted by telephone at 1 week and 1 month by the principal clinical investigator. Patients were asked about any persistent symptoms, repeat doctor visits, and ophthalmology referrals and if their vision had returned to normal. If patients had any concerns or persistent symptoms identified during the telephone calls they were asked to return for a follow-up examination by the principal investigator. Patients were asked to rate how effective they considered the study drug was on a numeric rating scale (NRS) between 0 and 10, with higher values indicating more effectiveness.

Measurements

Based on case reports there was a potential risk to participants of delayed healing, enlarged abrasion, recurrent corneal ulceration, toxic keratitis, surface keratopathy, corneal stromal infiltration, *Candida* and bacterial keratitis, uveitis, hypopyon, and corneal infiltrates.⁸⁻¹² We defined a complication as one of these specific findings.

The primary outcome of this study was to test the hypothesis that short-term use of topical anesthetics for corneal abrasions would be safe and would not affect corneal healing. Safety was measured based on persistent fluorescein uptake of the corneal abrasion at 48 hours and the occurrence rates of any complications. The lead investigator, a board-certified ED specialist consultant/attending reviewed charts daily and monitored for complications by reviewing 48-hour recheck examinations and any subsequent ophthalmology visits. The lead investigator also contacted patients by telephone and asked patients to return for additional examinations if there were any concerns. Any significant unexpected complication or adverse events would have resulted in premature ending of the study.

The secondary outcome of this study was to test the hypothesis that the use of topical anesthesia would reduce pain and be perceived as an effective treatment by patients suffering from corneal abrasions. This study measured pain scores using a 100-mm VAS and patients were asked to rate the overall effectiveness of the study drug on a NRS during two follow-up telephone interviews.

Data Analysis

We estimated that we could recruit 180 patients in 6 months based on injury numbers seen in the ED in previous years. Allowing for a 30% dropout rate identified in prior studies, this would provide 126 patients or two groups of 63 patients. The binomial probability confidence interval (CI) states that the chance of not seeing any complications specifically attributed to tetracaine use in 63 patients would be 0% to 5.7% at the 95% CI. A sample of 63 patients per group would also have 95% power (at the 0.05 level) to detect a minimum clinical difference in pain scores of 16 mm, on a 100-mm VAS, given a standard deviation of about 25 mm.

Data were analyzed using Stata version 12. The analysis was by chi-square tests on categorical end points for safety outcomes. No adjustments were made for multiple testing. No formal interim analyses of the data were carried out. Data were monitored by the medical research officer as patients were recruited into the study.

Unpaired t-test of the average pain score in each of the groups was measured and on the NRS of how effective the participants thought the treatment was. t-tests were also used on the continuous secondary endpoints. Separate analyses were done for each data collection time. A mixed model was used to simultaneously test the pain experience over the 48 hours that pain was measured. The mixed model was chosen as it extends normal regression models to allow for multiple measurements on individuals, as well as measurements on different individuals. The model adjusted for pain on arrival and allowed a different slope for the decay of pain over time for each individual. The VAS to measure acute pain has been validated and known to detect a minimal clinically significant difference of 16 mm.^{13,14}

RESULTS

The total number of patients eligible for inclusion into the study during the 12-month period was not recorded; however, a retrospective computer search identified 570 patients coded with corneal abrasions or corneal foreign bodies. Of these, 25 patients were under the consenting age, and an additional 155 patients were in the system twice for rechecks of the same injury. This left a possible eligible sample size of 390 patients.

The original trial registration was approved for 180 participants over a period of 6 months. Lower-than-expected recruitment rates resulted in an extension to the study to 1 year. After 1 year the trial was discontinued after recruiting 116 patients, rather than asking for an additional extension to recruit 10 more patients to reach the target of 126. A large number of patients were unwilling to be involved in the study mainly due

to the requirement to return for a 48-hour recheck (Figure 1).

A total of 122 patients were willing to be included into the study. Six patients who were enrolled and followed up were subsequently discovered to meet the exclusion criteria, and their data were removed from the analysis. These patients were incorrectly enrolled in the study as they were later diagnosed with conjunctivitis ($n = 2$), chronic defect from eye surgery ($n = 1$), and large corneal lacerations ($n = 3$).

The data of 116 patients were analyzed. Fifty-nine patients were randomized to receive tetracaine and 57 to receive saline. All patients had at least one follow-up contact. Eighty-one patients attended follow-up at 48 hours (69.8%). All of the remaining patients were subsequently contacted by telephone. Ninety-six patients (82.8%) were contacted at 1 week, and 103 (88.8%) were contacted at 1 month. Eighty-five patients returned pain questionnaires. We identified 11 patients who were noncompliant with the study protocols, four in the tetracaine group and seven in the saline group. Data analysis, however, was performed on all 116 patients enrolled into the study on an intention-to-treat analysis basis.

Table 2 shows the baseline demographics and clinical characteristics of the study participants. Baseline characteristics were similar in the tetracaine and saline groups. The majority of the patients presenting with corneal abrasions were male (93.2% tetracaine group, 86.9% saline group). Due to this, the results of the study have been presented as one group, as opposed to splitting the sample into male and female subgroups.

No complications specifically attributed to topical anesthetic use were identified in this study. This implies that the binomial probability CI of an uncommon complication specifically attributed to topical anesthetic use is 95% CI of 0% to 6.1%.

There were 23 patients with retained rust rings identified at the 48-hour recheck: 13 in the tetracaine group (13 of 59, 22.0%) and 10 in the saline group (10 of 57, 17.5%; risk difference 4.5%, 95% CI = -10% to 19%, $p = 0.544$). These patients' persistent symptoms were attributed to rust rings and repeated attempts to remove them, as opposed to the study drug. Their data were removed from analysis at 48 hours, 1 week, and 1 month, reducing the size of the sample to 46 in the tetracaine group and 47 in the saline group.

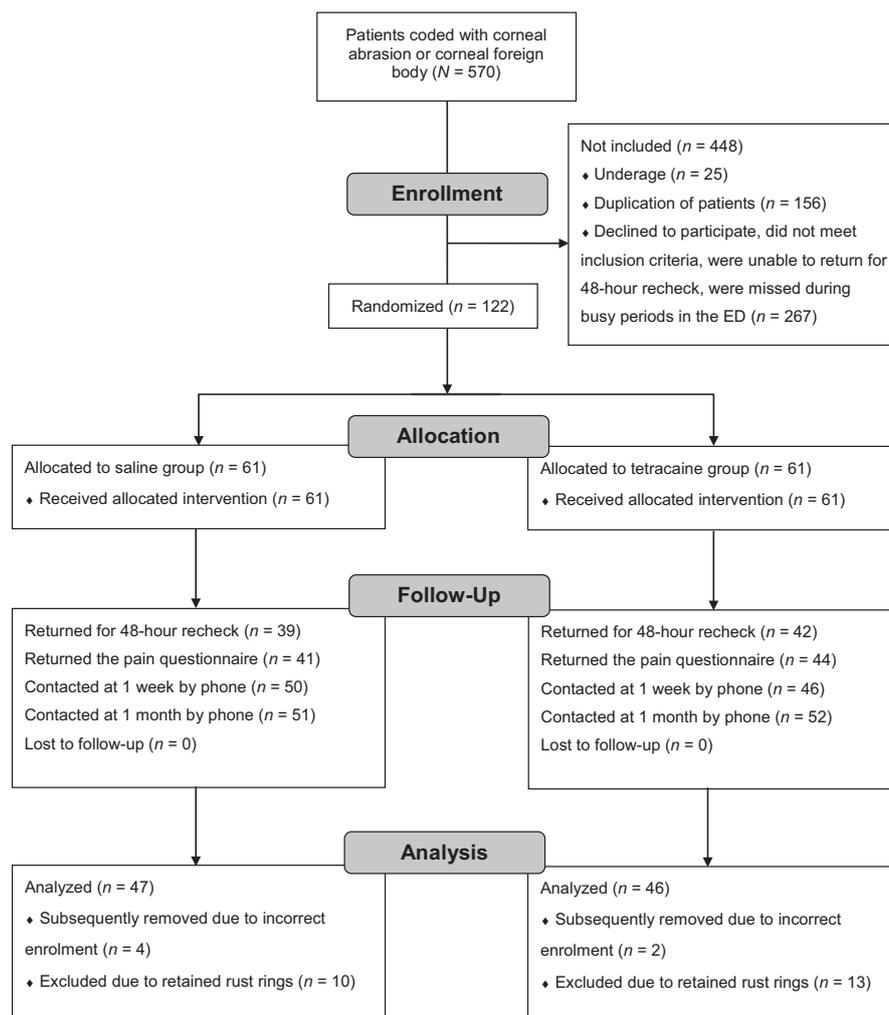


Figure 1. CONSORT flow diagram showing patient flow through the study.

Table 2
Baseline Demographics and Clinical Characteristics

Characteristic	Tetracaine (n = 59)	Saline (n = 57)
Age (yr), median (range)	37.0 (17*-72) years	38.0 (19-74) years
Sex		
Male	55 (93.2)	49 (86.0)
Female	4 (6.8)	8 (14.0)
Ethnicity		
European	37 (62.7)	32 (56.1)
Māori	4 (6.8)	4 (7.0)
Other	0	2 (3.5)
Did not answer	18 (30.5)	19 (33.3)
Mechanism of injury		
Metallic FB	30 (50.8)	30 (52.6)
Dirt FB	1 (1.7)	5 (8.8)
Dust FB	7 (11.9)	8 (14.0)
Wood FB	5 (8.5)	2 (3.5)
Direct trauma	8 (13.6)	7 (12.3)
Ultraviolet	3 (5.1)	0
Unknown	5 (8.5)	3 (5.3)
Other	0	2 (3.5)
Pain on arrival median (range, low-high)	(n = 32) 54.6 mm (10-98)	(n = 33) 48.0 mm (0-96)

*One 17-year-old patient enrolled with parental consent.
FB = foreign body.
Data are reported as n (%) unless otherwise stated.

At the 48-hour recheck there was no significant difference in healing identified by fluorescein uptake between the two groups. Fluorescein uptake was seen in 21 patients: 11 of 46 in the tetracaine group (23.9%) and 10 of 47 in the saline group (21.3%; risk difference = 2.6%, 95% CI = -14% to 20%, p = 0.761). There were 12 patients who had fluorescein uptake at 48 hours but did not present with any other symptoms (five tetracaine, seven saline).

There were a total of 20 patients with persistent symptoms at the 48-hour rechecks. Ten of 46 were identified in the tetracaine group (21.7%) and 10 of 47 in the saline group (21.3%); there was no statistical difference in the number of persistent symptoms between the two

Table 3
Persistent Symptoms at 48 Hours and 1 Week

Complaint	Tetracaine Group		Saline Group	
	48 Hours (n = 10)	1 Week (n = 1)	48 Hours (n = 10)	1 Week (n = 4)
Pain	3	0	0	2
Irritation	4	0	7	2
Photophobia	1	0	2	1
Blurriness	0	0	1	1
Redness	5	1	5	0
Dryness	0	0	1	1

groups (risk difference = 0.4%, 95% CI = -16% to 17%, p = 0.957). The persistent symptoms are listed in Table 3. At 1 week, persistent symptoms were identified in five patients, one in the tetracaine group (2.2%) and four in the saline group (8.5%; risk difference = 6.3%, 95% CI = -3% to 15%, p = 0.176; Table 3).

Five patients were identified who required additional examination and treatment, and their specific complaints and outcomes are shown in Table 4. Two patients were identified in the tetracaine group (of 46, 4.3%) and three in the saline group (of 47, 6.4%); there was no statistical difference in the number of patients requiring additional examinations between the two groups (risk difference = 2.1%, 95% CI = -7% to 11%, p = 0.664).

At 1 month, when patients were contacted by telephone, no complications were reported by either group; however, one patient in the saline group had persistent irritation and one patient in the tetracaine group had some slight blurring of the vision.

Eighty-five patients returned pain questionnaires (44 tetracaine group, 41 saline group). In the questionnaire 65 patients provided their pain scores on arrival at the ED (32 tetracaine group, 33 saline group). Subjects in the tetracaine group had a median pain score on arrival at the ED of 54.6 mm on the VAS (range = 10 to 98 mm) while subjects in the saline group had a median pain score of 48.0 mm (range = 0 to 96 mm). Not all patients recorded pain scores at any given time. Figure 2 shows

Table 4
Patients Requiring Additional Examination and Treatment

Complaint	Outcome
Tetracaine group (n = 2)	
No pain, but persistent redness and blurry vision.	Ophthalmologist felt that the corneal abrasion was actually a partial-thickness corneal laceration. Small white infiltrate that was scraped with no growth. Received Cipro eye drops. Small scar and normal healing by 10 days.
Patient saw a small white spot in the eye.	Asked to return; on examination an asymptomatic small opaque scar was identified. No further treatment was required.
Saline group (n = 3)	
Itchy eye with occasional foreign body sensation.	Reexamined and found to have a normal cornea. Dry eyes and symptoms resolved with artificial tears. No further treatment necessary.
Photophobia, pain, and redness at 1 week.	Reexamined and found to have a fluorescein uptake and erythema. Ophthalmologist diagnosed patient with recurrent corneal erosion.
Photophobia and headaches in sunlight.	Reexamined and found to have normal cornea. Advised to avoid bright sunlight and take analgesia. Patient was seen at 1 month with normal examination but slightly blurry vision; advice given to see an optician for corrective lenses.

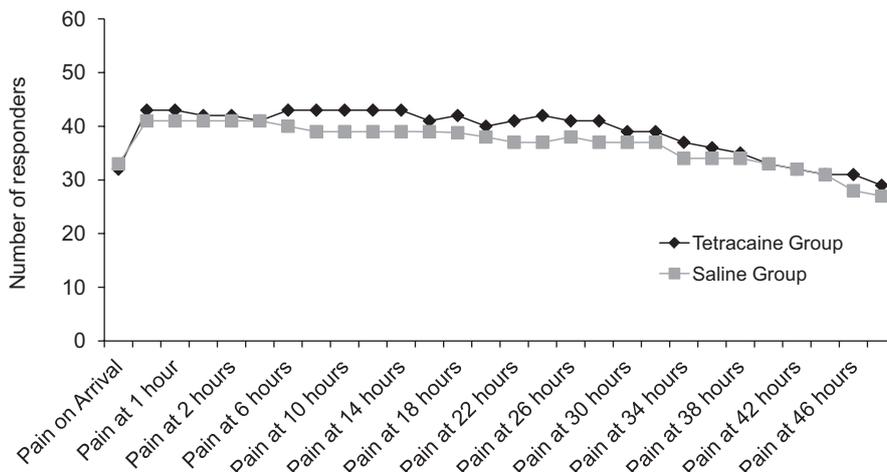


Figure 2. The number of responders to the pain score questionnaire over the 48-hour study period.

the number of patients who responded at each given time point. Figure 3 shows the box plot of VAS pain scores of all the participants over the 48-hour study period.

We were unable to show a clinically significant difference in pain scores at any given time between the tetracaine and the saline group. The average difference in pain over the first 24 hours was 0.44 mm on a 100-mm VAS pain scale (95% CI = -0.32 to 1.20, $p = 0.259$). The average difference in pain over the 48-hour period between the groups was 0.53 on a 100-mm VAS pain scale (95% CI = -0.19 to 1.24, $p = 0.149$). Both of these results were clinically insignificant. All of the pain scores were analyzed simultaneously using a mixed model approach to adjust for the fact that there were repeated measures on individuals, adjusted for pain on

arrival, and allowing for individuals with different pain levels and pain reducing at different rates.

Patients were contacted by telephone by the principal clinical investigator at 1 week and were asked how effective they felt the drug that they had been given was. Patients were asked to rate the study drug’s effectiveness on a NRS between 0 and 10, with higher values indicating more effectiveness. Responses were received from 80 patients (39 tetracaine, 41 saline). Patients in the tetracaine group scored the study drug 7.7 on the NRS, while those in the saline group scored the study drug 3.8 (difference = 3.9, 95% CI = 2.4 to 5.3, $p < 0.0005$). To ensure that this figure was accurate, the patients were asked the same question one month later as a test of repeatability. Seventy-three patients answered the question at 1 month (37 tetracaine, 36

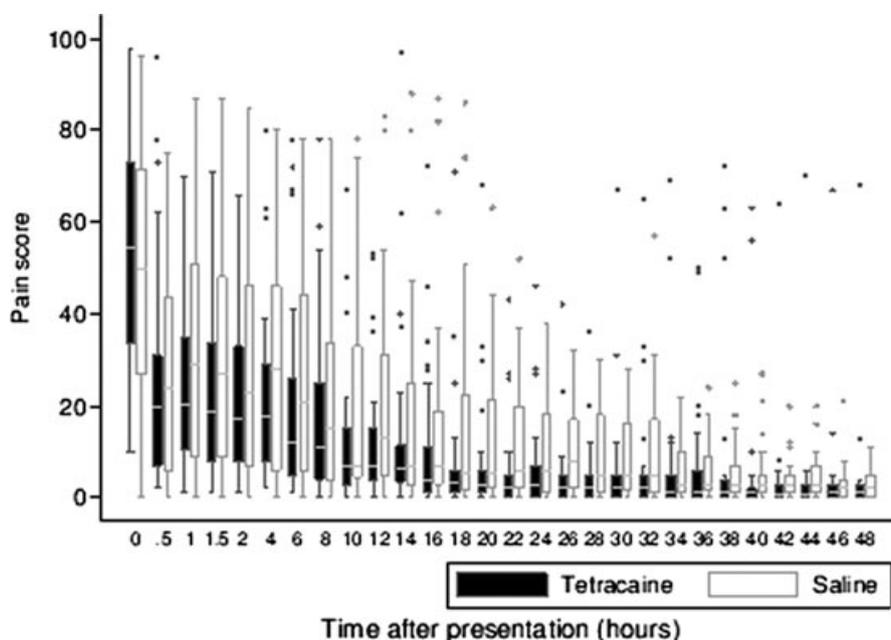


Figure 3. Box plot of VAS pain scores of all the participants over the 48-hour study period. The box contains data that lie between the 25th and 75th percentiles. The line through the box shows the median. The whiskers show data out to the 95th percentile. Data outside of the 95th percentile are dots or diamonds. VAS = visual analogue scale.

saline): the tetracaine group scored the effectiveness 7.8 on the NRS, while those in the saline group scored the effectiveness at 3.7 (difference = 4.0, 95% CI = 2.5 to 5.6, $p < 0.0005$). These results show the reliability of this answer and demonstrate a statistically significant difference between the tetracaine and saline groups ($p < 0.0005$).

DISCUSSION

Topical anesthetics have been shown to be toxic to the corneal epithelium in laboratory experiments on animals. Toxic effects include direct toxicity to cytoskeletal structures and cellular function, as well as indirect toxicity causing the loss of epithelial microvilli, which leads to tear film instability, desiccation, and inhibition of reepithelialization.^{8,10,12} Disruption of the surface microvilli of the epithelial cells causes a decrease in mucus adherence, poor wettability of the cornea, and shortening of tear break-up time.⁸ Blocking the natural tear production reflex to noxious stimuli causes tear production and blinking rates to decrease.⁸ In addition, topical anesthetics are thought to cause an increase in corneal permeability and swelling, which may result in a loss of corneal transparency.¹² Increased epithelial sloughing rates have also been demonstrated, suggesting decreased adherence of the epithelial cells and delayed healing.⁸

A 1996 study reviewed laboratory animal studies of delayed healing and showed that these studies were “predominantly designed to highlight problems of acute toxicity or to demonstrate chronic effects on tissue wound healing.”¹¹ In many of these studies there was no attempt at corneal healing in the animal.^{4,11} It is possible that these animal studies that examined toxicity and minute changes may not be clinically relevant to humans; for example, the loss of microvilli seen in experiments on human cadavers may not be found in vivo.¹¹ Rabbits have a more sensitive cornea and reduced baseline blinking rate when compared to humans, which makes the generalization of these findings to the human cornea questionable.^{15,16} Two rabbit studies, one using 0.01% lidocaine and the other 0.05% proparacaine administered in a controlled fashion, did not demonstrate harmful effects, even with continuous infusion.^{15,16}

Concerns regarding human complications are based on case reports describing the unsupervised, prolonged use of topical anesthetics. Most of these reports are at least 25 years old and Verma and Marshall¹¹ suggest that the medications used were high doses from 10-mL dropper bottles that contained preservatives. These complications occurred with repeated high doses in an unsupervised fashion.^{4,11}

The first studies to question whether the histopathologic effects seen in animal studies would be clinically important to humans using the medication in a supervised fashion were done by eye surgeons using topical anesthetics for pain control after PRK surgery.^{3,4,11} In two studies (38 and 44 patients), none of the patients had delayed healing at 72 hours.^{3,4} Two additional studies in EDs investigated the use of topical anesthetics after corneal abrasions. Recruitment in these studies

was limited (47 patients, 31 patients) and although the results showed no serious complications and a reduction of pain, many patients did not have adequate follow-up, and the studies were underpowered to prove safety and efficacy.^{5,6}

This current study found no complications specifically attributed to topical anesthetic use. There was no significant difference in healing identified by fluorescein uptake between the two groups, which is similar to the findings of previous smaller studies.³⁻⁶ No statistically significant difference was found between the number of patients with persistent symptoms at 48 hours and at 1 week. The persistent symptoms that were identified at 48 hours and 1 week (Table 3) were all minor in nature and were not unexpected. Similar symptoms were identified in both groups. Similar to our study, Verma et al.³ did not show any significant disturbances of epithelial healing, refractive outcome, or visual performance. The safety demonstrated in this study is similar to that found in studies by Verma and colleagues,^{3,4,11} Ball and colleagues,⁶ and Ting and colleagues.⁵

Topical tetracaine did not cause any complications previously attributed to topical anesthetic use in the 59 patients of the treatment arm in this study. The binomial probability CI of the incidence of these uncommon complications occurring is 95% CI of 0% to 6.1%. Although this study found a zero complication rate, we can only state that the complication rate must be less than 6.1%, and defining a drug as “safe” or deciding upon an acceptable low level of complications is subjective.

Retained rust rings were common in both the tetracaine ($n = 13$) and saline groups ($n = 10$). The large number of patients with retained rust rings was an unexpected finding for the researchers and made it difficult to analyze the data. All but one of these patients had persistent symptoms at 48 hours or 1 week. Of the patients with rust rings, fluorescein uptake was seen in four of the 10 in the saline group and seven of the 13 in the tetracaine group. We attributed the fluorescein uptake and persistent symptoms to the retained rust rings, as opposed to the study drug. Although the data from 48 hours, 1 week, and 1 month were not analyzed, all of these patients were monitored for complications or additional eye visits and follow-up was completed on all of these patients. Sending a patient home with tetracaine drops did not mask any symptoms of the retained rust rings, cause any complications, or prevent patients from returning for additional care. The lack of any complications or statistical differences in fluorescein uptake, persistent symptoms at 48 hours, or persistent symptoms at 1 week or at 1 month has led us to conclude that the use of tetracaine was safe for limited half-hourly use for 24 hours.

In contrast to other ED studies^{5,6} where recruitment numbers were low and follow-up was incomplete, this study recruited considerably larger numbers, follow-up was obtained on 100% of the patients, and we believe it to be one of the largest studies of its type to date. The results of this study confirm prior smaller studies and, given the large recruitment numbers, provides robust results.

Visual analogue scores in both groups reduced to below 10 mm after 12 hours and approached zero after

24 hours of healing and after the tetracaine usage was stopped. This may be due to the simple fact that the majority of corneal abrasion pain goes away completely by about 24 hours. This may have made it nearly impossible to show a clinically significant difference in pain relief over the full 48-hour period, especially given the sample size. While the study was not designed to do a breakdown of pain over shorter periods of time, a post hoc look at this made sense, but no significant difference was seen during any time period.

We were unable to detect a clinically significant difference in VAS pain scores between the two groups but identified a large difference in effectiveness from the NRS score. There may be a number of explanations for this. First, the effect of tetracaine might have worn off fast enough that the pain scores were not reduced, but the sensation of rapid relief from the tetracaine, even though transient, may have led to the perception of greater effectiveness. Second, patients have been shown to respond to placebo distracters: since tetracaine burns a bit on instillation, the perception of effectiveness may be artificial—"it burns, it must be strong." These are reasons that we cannot discount. This study's inability to demonstrate a difference in pain scores is in contrast to a study of PKR surgery by Verma and Marshall,¹¹ where they "demonstrated that topical tetracaine 1% administered at half hourly intervals for 24 hours was effective in controlling pain."

The Southland area of New Zealand is a farming community and the researchers felt that local culture was very stoic and reluctant to complain about pain. We believe that this is reflected in the current study, as the baseline pain scores were low for both groups and we were unable to show a clinically significant difference in pain scores at any given time point. When asked to rate the study drug's effectiveness on a 0 to 10 NRS, patients rated the two drugs' effectiveness quite differently. The researchers felt that in contrast to the VAS pain scale, the NRS question gave stoic patients the opportunity to express their feelings about the drug without specifically complaining of pain or showing weakness. At 1 week, patients in the tetracaine group scored the study drug on average 7.7 compared to patients in the saline group 3.8. A 2010 study by Ball and colleagues⁶ recorded patient satisfaction scores for their study drug (diluted proparacaine) and had similar findings to our NRS scores. The authors feel that the patients' NRS effectiveness ratings at 1 week and 1 month for the study drug were equally as important as the VAS pain scores.

LIMITATIONS

This study specifically excluded penetrating eye injuries, large or complicated corneal abrasions, and injuries causing a significant disruption of vision. We also excluded patients suffering from infectious or chemical conjunctivitis or ocular infections or those who had grossly contaminated foreign bodies in their eyes. It would not be safe to assume that the treatment for a simple corneal abrasion could be generalized to these more complicated conditions.

Some patients discovered when using the tetracaine drops that they experienced burning similar to the tetracaine they were treated with in the ED. Some patients, when contacted for follow-up, commented on the drops burning. This may have inadvertently unblinded the patient and researcher to what drugs they were taking, but was unavoidable.

It is possible that some patients may have been able to recognize the difference between the saline bullets and the tetracaine vials, but this did not seem to occur. It is possible but unlikely that the doctor enrolling the patient into the study may have been able to detect a difference in the weight or shape of the envelope contents, but this was irrelevant to the results as they were not involved in any subsequent data collection.

Patient compliance with administering the tetracaine or the saline or when taking paracetamol was not recorded. Patients were sent home with instructions to take paracetamol and tetracaine or saline drops. They were asked on the pain questionnaire when they took their last dose of paracetamol, but patient compliance at documenting this was poor. It was not specifically asked if they took the study drug as directed. It is not known if there was a difference between the compliance of the two groups.

The study may have been underpowered to detect a difference in efficacy between the two groups because it was terminated prior to reaching the calculated sample size. Convenience sampling may have resulted in eligible patients being missed during busy periods.

We employed an intention-to-treat analysis, which may have confounded the results. Eleven patients were identified as being noncompliant, and using intention-to-treat analysis these patients had their data analyzed. Under a different study design these patients may have been removed.

A limitation of using a mixed-model statistical analysis is the assumption that the residuals are normally distributed. This limitation is less important as the numbers in the analysis increase. In this study the residuals may not be normally distributed as many people said that they had no pain. The results of these models should be treated cautiously.

Our ability to assess corneal healing at 48 hours was based on standard ED equipment and was limited to fluorescein staining with slit-lamp examination. We did not employ sophisticated optical devices to detect healing abnormalities on a microscopic level. Furthermore, the ability to detect the complications was limited by the physicians performing the follow-up; not all patients were examined by an emergency specialist or ophthalmologist, and it is possible that complications were missed or developed later. However, we feel confident that all complications were identified as all patients were followed up at some time point, and the authors believe that it is unlikely that any clinically important complications were missed.

CONCLUSIONS

Clinicians wanting to send patients home with topical anesthetics for pain relief after corneal abrasions have avoided doing so for fear of potential complications.

This study shows that tetracaine drops are safe to use for the short duration. While tetracaine eye drops were not found to provide greater pain relief as measured by a visual analogue scale over time, patients rated the tetracaine as more effective than saline in overall effectiveness surveys. The researchers recommend that the short-term use of tetracaine eye drops for 24 hours for pain relief from simple corneal abrasions should become routine practice.

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