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Topical ophthalmic anesthetics for corneal abrasions (Review)

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Sulewski M, Leslie L, Liu S-H, Ifantides C, Cho K, Kuo IC.
Topical ophthalmic anesthetics for corneal abrasions.
Cochrane Database of Systematic Reviews 2023, Issue 8. Art. No.: CD015091.
DOI: 10.1002/14651858.CD015091.pub2.

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[Intervention Review]

Topical ophthalmic anesthetics for corneal abrasions

Michael Sulewski[1], Louis Leslie[2], Su-Hsun Liu[2,3], Cristos Ifantides[2], Kyongjin Cho[4], Irene C Kuo[1]

[1]Wilmer Eye Institute, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. [2]Department of Ophthalmology, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA. [3]Department of Epidemiology, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA. [4]Department of Ophthalmology, Dankook University, College of Medicine, Cheonan, Korea, South

Contact: Irene C Kuo, ickuo@jhmi.edu.

Editorial group: Cochrane Eyes and Vision Group.
Publication status and date: Edited (no change to conclusions), published in Issue 10, 2023.

Citation: Sulewski M, Leslie L, Liu S-H, Ifantides C, Cho K, Kuo IC. Topical ophthalmic anesthetics for corneal abrasions. *Cochrane Database of Systematic Reviews* 2023, Issue 8. Art. No.: CD015091. DOI: 10.1002/14651858.CD015091.pub2.

ABSTRACT

Background

Despite potential analgesic benefits from topical ophthalmic amides and esters, their outpatient use has become of concern because of the potential for abuse and ophthalmic complications.

Objectives

To assess the effectiveness and safety of topical ophthalmic anesthetics compared with placebo or other treatments in persons with corneal abrasions.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; Embase.com; Latin American and Caribbean Health Sciences (LILACS); ClinicalTrials.gov; and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), without restriction on language or year of publication. The search was performed on 10 February 2023.

Selection criteria

We included randomized controlled trials (RCTs) of topical ophthalmic anesthetics alone or in combination with another treatment (e.g. nonsteroidal anti-inflammatory drugs (NSAIDs)) versus a non-anesthetic control group (e.g. placebo, non-treatment, or alternative treatment). We included trials that enrolled participants of all ages who had corneal abrasions within 48 hours of presentation.

Data collection and analysis

We used standard Cochrane methodology.

Main results

We included nine parallel-group RCTs with a total of 556 participants (median number of participants per study: 45, interquartile range (IQR) 44 to 74), conducted in eight countries: Australia, Canada, France, South Korea, Turkey, New Zealand, UK, and USA.

Study characteristics and risk of bias

Four RCTs (314 participants) investigated post-traumatic corneal abrasions diagnosed in the emergency department setting. Five trials described 242 participants from ophthalmology surgery centers with post-surgical corneal defects: four from photorefractive keratectomy (PRK) and one from pterygium surgery. Study duration ranged from two days to six months, the most common being one week (four RCTs). Treatment duration ranged from three hours to one week (nine RCTs); the majority were between 24 and 48 hours (five RCTs). The age of

participants was reported in eight studies, ranging from 17 to 74 years of age. Only one participant in one trial was under 18 years of age. Of four studies that reported funding sources, none was industry-sponsored. We judged a high risk of bias in one trial with respect to the outcome pain control by 48 hours, and in five of seven trials with respect to the outcome complications at the furthest time point. The domain for which we assessed studies to be at the highest risk of bias was missing or selective reporting of outcome data.

Findings

The treatments investigated included topical anesthetics compared with placebo, topical anesthetic compared with NSAID (post-surgical cases), and topical anesthetics plus NSAID compared with placebo (post-surgical cases).

Pain control by 24 hours

In all studies, self-reported pain outcomes were on a 10-point scale, where lower numbers represent less pain. In post-surgical trials, topical anesthetics provided a moderate reduction in self-reported pain at 24 hours compared with placebo of 1.28 points on a 10-point scale (mean difference (MD) −1.28, 95% confidence interval (CI) −1.76 to −0.80; 3 RCTs, 119 participants). In the post-trauma participants, there may be little or no difference in effect (MD −0.04, 95% CI −0.10 to 0.02; 1 RCT, 76 participants). Compared with NSAID in post-surgical participants, topical anesthetics resulted in a slight increase in pain at 24 hours (MD 0.82, 95% CI 0.01 to 1.63; 1 RCT, 74 participants).

One RCT compared topical anesthetics plus NSAID to placebo. There may be a large reduction in pain at 24 hours with topical anesthetics plus NSAID in post-surgical participants, but the evidence to support this large effect is very uncertain (MD −5.72, 95% CI −7.35 to −4.09; 1 RCT, 30 participants; very low-certainty evidence).

Pain control by 48 hours

Compared with placebo, topical anesthetics reduced post-trauma pain substantially by 48 hours (MD −5.68, 95% CI −6.38 to −4.98; 1 RCT, 111 participants) but had little to no effect on post-surgical pain (MD 0.41, 95% CI −0.45 to 1.27; 1 RCT, 44 participants), although the evidence is very uncertain.

Pain control by 72 hours

One post-surgical RCT showed little or no effect of topical anesthetics compared with placebo by 72 hours (MD 0.49, 95% CI −0.06 to 1.04; 44 participants; very low-certainty evidence).

Proportion of participants with unresolved epithelial defects

When compared with placebo or NSAID, topical anesthetics increased the number of participants without complete resolution of defects in trials of post-trauma participants (risk ratio (RR) 1.37, 95% CI 0.78 to 2.42; 3 RCTs, 221 participants; very low-certainty evidence). The proportion of placebo-treated post-surgical participants with unresolved epithelial defects at 24 to 72 hours was lower when compared with those assigned to topical anesthetics (RR 0.14, 95% CI 0.01 to 2.55; 1 RCT, 30 participants; very low-certainty evidence) or topical anesthetics plus NSAID (RR 0.33, 95% CI 0.04 to 2.85; 1 RCT, 30 participants; very low-certainty evidence).

Proportion of participants with complications at the longest follow-up

When compared with placebo or NSAID, topical anesthetics resulted in a higher proportion of post-trauma participants with complications at up to two weeks (RR 1.13, 95% CI 0.23 to 5.46; 3 RCTs, 242 participants) and post-surgical participants with complications at up to one week (RR 7.00, 95% CI 0.38 to 128.02; 1 RCT, 44 participants). When topical anesthetic plus NSAID was compared with placebo, no complications were reported in either treatment arm up to one week post-surgery (risk difference (RD) 0.00, 95% CI −0.12 to 0.12; 1 RCT, 30 participants). The evidence is very uncertain for safety outcomes.

Quality of life

None of the included trials assessed quality of life outcomes.

Authors' conclusions

Despite topical anesthetics providing excellent pain control in the intraoperative setting, the currently available evidence provides little or no certainty about their efficacy for reducing ocular pain in the initial 24 to 72 hours after a corneal abrasion, whether from unintentional trauma or surgery. We have very low confidence in this evidence as a basis to recommend topical anesthetics as an efficacious treatment modality to relieve pain from corneal abrasions. We also found no evidence of a substantial effect on epithelial healing up to 72 hours or a reduction in ocular complications when we compared anesthetics alone or with NSAIDs versus placebo.

PLAIN LANGUAGE SUMMARY

What are the benefits and unwanted effects of topical anesthetics for corneal abrasions?

Key message(s)

1. We are very uncertain about the effectiveness of anesthetic eye drops for control of pain due to corneal abrasions (scratches).

2. We are very uncertain about the safety of anesthetic eye drops regarding speed of healing and complications.

3. To ensure trustworthy evidence, researchers should follow best-practice guidance. Future research studies should include more people followed over a longer period of time after treatment ends.

What is a corneal abrasion?

A corneal abrasion is a scratch on the clear outer layer of the eye. These scratches can be caused by fingernails, dust, dirt, wood, twigs, thorns, or metal shavings blown or pushed into the eye. Improper use of contact lenses sometimes results in minor but painful scratches on the cornea. Some eye surgeries, like one type of laser refractive surgery, may require deliberately creating an abrasion. The symptoms of corneal abrasion include eye pain, blurred vision, grittiness, excessive tearing, redness, light sensitivity, or even headache.

How are corneal abrasions treated?

Non-medicine-based care of corneal abrasions includes eye rinse with clean water or normal saline and frequent blinking. Although most minor scratches on the cornea can heal on their own, they are typically treated with antibiotic eye drops or ointment to prevent infections. Sometimes, doctors prescribe topical painkillers to reduce eye pain, such as anesthetics (medications that lower the sense of pain) and nonsteroidal anti-inflammatory drugs (NSAIDs).

What did we want to find out?

We assessed whether anesthetic eye drops reduce pain in people with corneal abrasions. We also examined whether anesthetic eye drops influence the healing of the corneal wound or cause unwanted effects on the eyes.

What did we do?

We performed a systematic review by searching for studies that compared anesthetic eye drops with no treatment, inactive eye drops, or a different medication. We summarized the review findings and reported results along with our confidence about the evidence based on the study design and method.

What did we find?

We found nine studies that had enrolled 556 people aged 17 years or older. Four studies took place in hospital emergency care settings and five took place in eye surgery settings. Most studies were one week long, but their length ranged from two days (one study) to six months (another study). Only four studies reported funding sources, none of which were drug companies.

In comparison with inactive treatment, anesthetic eye drops alone were effective in reducing eye pain up to 24 hours after treatment and may also be effective when combined with NSAIDs. When compared with NSAIDs, the anesthetic eye drops alone were slightly less effective at pain control. At 48 hours, anesthetics alone decreased eye pain relative to inactive eye drops but were no more effective at 72 hours. Anesthetic eye drops resulted in a slight delay in wound healing up to 72 hours after treatment. Other complications, such as infections, were slightly more frequent with anesthetics, but these complications were similar between groups up to one week after treatment. There were too few studies to know whether people responded to treatment differently when the abrasion was from an injury or from eye surgery. No study looked at quality of life.

The evidence for all outcomes in this review is very uncertain. Further research studies that enroll larger numbers of participants and follow them for at least one week are likely to change our findings.

What are the limitations of the evidence?

We are not confident of the conclusions suggested by the evidence found for this review of the effectiveness and safety of anesthetic eye drops because of the flawed collection and reporting of data, and the small size of the studies.

How up-to-date is this evidence?

The evidence is up-to-date as of 10 February 2023.

Summary of findings 1. Topical ophthalmic anesthetic compared with placebo or NSAID

Topical ophthalmic anesthetic compared with placebo or NSAID

Patients or population: corneal abrasion (post-trauma or post-surgical)

Settings: emergency department or ophthalmology surgery

Intervention: anesthetic (tetracaine, proparacaine, lidocaine)

Comparison: placebo or NSAID (diclofenac, artificial tears, saline)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (RCTs)	Certainty of the evidence (GRADE)	Comments
	Assumed risk with comparator	Corresponding risk with anesthetic				
Changes in mean participant-reported ocular pain from baseline to 24 hours Assessed with: VAS pain intensity 0 to 10	**Placebo, post-surgery**				⊕⊖⊖⊖ Very low[a,b]	Lower is better. The original VAS was from 0 to 100 in Waldman 2014, which compared tetracaine 1% with placebo in post-trauma participants.
	The mean change in the comparison group was 3.63 (SD 1.00)	The mean change in the intervention group was 1.28 lower (0.80 to 1.76)	—	119 (3 RCTs)		
	Placebo, post-trauma (see comment)					
	The mean change in the comparison group was 0.11 (SD 0.13)	The mean change in the intervention group was 0.04 lower (0.10 lower to 0.02 higher)	—	76 (1 RCT)		
	NSAID, post-surgery					
	The mean change in the comparison group was 2.09 (SD 1.77)	The mean change in the intervention group was 0.82 higher (0.01 to 1.63)	—	74 (1 RCT)		
Changes in mean participant-reported ocular pain from baseline to 48 hours Assessed with: VAS pain intensity 0 to 10	**Placebo, post-surgery**				⊕⊖⊖⊖ Very low[a,b,c]	Lower is better. Waldman 2014 was excluded from the analysis due to missing data.
	The mean change in the comparison group was 0.81 (SD 1.46)	The mean change in the intervention group was 0.41 higher (0.45 lower to 1.27 higher)	—	44 (1 RCT)		
	Placebo, post-trauma					

	The mean change in the comparison group was 7.23 (SD 1.95)	The mean change in the intervention group was 5.68 lower (4.98 lower to 6.38 lower)	—	111 (1 RCT)		
Changes in mean participant-reported ocular pain from baseline to 72 hours Assessed with: VAS pain intensity 0 to 10	The mean change in the comparison group was 0.2 (SD 0.83)	The mean change in the intervention group was 0.49 higher (0.06 lower to 1.04 higher)	—	44 (1 RCT)	⊕⊖⊖⊖ Very low[b,c,d]	Lower is better. Only Verma 1995 reported pain outcomes beyond 48 hours (at 64 hours).
Proportion of participants without complete resolution of epithelial defects by 24 to 72 hours	**Placebo, post-trauma**				⊕⊖⊖⊖ Very low[b,c,e]	RR < 1 is better. Another post-surgery trial (44 participants) reported no events in either arm.
	152 per 1000	208 per 1000 (118 to 367)	RR 1.37 (0.78 to 2.42)	221 (3 RCTs)		
	Placebo, post-surgery					
	200 per 1000	28 per 1000 (2 to 510)	RR 0.14 (0.01 to 2.55)	30 (1 RCT)		
Proportion of participants with complications at longest time point Up to 2 weeks	**Placebo, post-trauma**				⊕⊖⊖⊖ Very low[a,c,f]	RR < 1 is better. Two post-surgical trials (75 participants) and one post-trauma trial (33 participants) reported no events in either arm.
	65 per 1000	73 per 1000 (15 to 355)	RR 1.13 (0.23 to 5.46)	242 (3 RCTs)		
	Placebo, post-surgery					
	19 per 1000 (1 to 356)	136 per 1000**	7.00 (0.38 to 128.02)	44 (1 RCT)		

*The basis for the **assumed risk** is the mean baseline risk from the studies in the meta-analysis; the total number of events in the control group divided by the total number of participants in the control groups, scaled to 1000. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**The corresponding risk was the absolute risk (number of events divided by number of participants in the intervention group). The 95% CI was calculated using a binomial distribution.

CI: confidence interval; **MD:** mean difference; **NSAID:** nonsteroidal anti-inflammatory drug; **RR:** risk ratio; **SD:** standard deviation; **VAS:** visual analog scale

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low-certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded for serious risk of bias (−2 levels).
[b]Downgraded for imprecision (−1 level).
[c]Downgraded for indirectness (−1 level).
[d]Downgraded for risk of bias (−1 level).
[e]Downgraded for inconsistency (−1 level).
[f]Downgraded for extreme imprecision (−2 levels).

Summary of findings 2. Topical ophthalmic anesthetic plus NSAID compared with placebo

Topical ophthalmic anesthetic plus NSAID compared with placebo

Patients or population: corneal abrasion (post-surgical)

Settings: ophthalmology surgery

Intervention: anesthetic with NSAID (proparacaine plus diclofenac)

Comparison: placebo (artificial tears)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (RCTs)	Certainty of the evidence (GRADE)	Comments
	Assumed risk with placebo	Corresponding risk with anesthetic plus NSAID				
Changes in mean participant-reported ocular pain from baseline to 24 hours VAS (scale 0 to 10)	The mean change in the comparison group was 8.08 (SD 2.28)	The mean change in the intervention group was 5.72 lower (4.09 lower to 7.35 lower)	—	30 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]	Lower is better.
Changes in mean participant-reported ocular pain from baseline to 48 hours	—	—	—	—	—	—
Changes in mean participant-reported ocular pain from baseline to 72 hours	—	—	—	—	—	—

Proportion of participants without complete resolution of epithelial defects by 24 to 72 hours	200 per 1000	66 per 1000 (8 to 570)	RR 0.33 (0.04 to 2.85)	30 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]	RR < 1 is better.
Proportion of participants with complications at longest time point Up to 1 week	No adverse events reported in either arm.		—	30 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]	RR < 1 is better.

*The basis for the **assumed risk** is the mean baseline risk from the studies in the meta-analysis; the total number of events in the control group divided by the total number of participants in the control groups, scaled to 1000. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **NSAID:** nonsteroidal anti-inflammatory; **RR:** risk ratio; **SD:** standard deviation; **VAS:** visual analog scale

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate-certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low-certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low-certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded for risk of bias (−1 level).
[b]Downgraded for extreme imprecision (−2 levels).

BACKGROUND

Description of the condition

Corneal abrasions (also known as corneal epithelial defects) are lamellar losses of the corneal epithelium, the superficial, regenerative, squamous barrier of the cornea (Nishida 2022). Etiologies of abrasions include accidental trauma (mechanical, chemical, or phototoxic), ocular surgery, corneal dryness, exposure (inadequate eyelid coverage of the cornea), neurotrophic disease, ocular inflammation, infection, as well as a variety of other intrinsic ocular pathologies (Nishida 2022). Corneal abrasion is a common emergency, representing about 13% of eye-related emergency department visits in the United States (Channa 2016; Vaziri 2016), with an estimated annual incidence of 3 per 1000 persons and a roughly two-to-one male predominance according to the National Ambulatory Medical Care Survey (NAMCS) (McGwin 2005). Globally an estimated 55 million eye injuries occur each year, with 750,000 requiring hospitalization (Négrel 1998).

Abrasions resulting from trauma may inoculate the eye with foreign matter and microbial organisms, leading to corneal infection. Symptoms of a corneal abrasion include intense pain, photophobia, redness, and tearing. Depending on the healthcare setting, corneal abrasions may be diagnosed and initially treated by primary care physicians, emergency medicine providers, or eye care specialists (Ahmed 2015). On clinical examination, corneal epithelial defects are best visualized by instilling fluorescein dye into the tear film, which adheres to bare stroma (but not intact epithelium), and emits a green fluorescence when illuminated with cobalt-blue filtered light (Martonyi 2022). In an emergency setting, an examination is performed with a slit lamp biomicroscope or penlight to identify other complicating factors such as microbial infection (manifested as a corneal infiltrate), corneal laceration (deep injury beyond the corneal epithelium), or the presence of a foreign body (Hamill 2022).

In contrast to trauma, the creation of a corneal epithelial defect is the intended consequence of many commonly performed ocular surgeries, including photorefractive keratectomy (PRK, a laser refractive procedure), superficial keratectomy (removal of anterior corneal lesions), and the epithelium-off variations of corneal cross-linking (a treatment for keratoconus). Unlike accidental trauma, abrasions created in the setting of ocular surgery derive benefit from a sterile field. Often, adjunctive treatments such as intraoperative topical mitomycin-C (an anti-metabolite) and postoperative steroids are used to reduce postoperative inflammation and scarring. Bandage contact lenses are typically applied for patient comfort after these types of procedures and are removed when the cornea re-epithelializes (Chuck 2018; Garcia-Ferrer 2019).

The human cornea is one of the most densely innervated tissues, with an estimated density of approximately 7000 nerve terminals per square millimeter (Nishida 2022). Approximately 20% of corneal nociceptors are mechanoreceptors that generate acute pain (Shaheen 2014). Regardless of the cause of a corneal abrasion, the dense network of sensory nerve endings in the cornea may result in intense eye pain until the corneal epithelial defect is healed (Marfurt 2010; Nishida 2022). In a healthy eye, most such defects heal fully in 24 to 48 hours by peripheral migration of sheets of epithelial cells, ultimately derived from the limbal epithelial stem cells (Hamill 2022); topical antibiotic is almost always prescribed to prevent infection. Although healing often occurs without permanent damage to the cornea, potential complications include recurrent corneal erosions, infectious keratitis, corneal scarring, thinning of the corneal stroma, or corneal perforation. These events may require intensive medical or surgical management and can lead to vision loss or loss of the eye. The mainstays of treatment for a corneal abrasion are infection prophylaxis and pain control, coupled with close outpatient follow-up (Hamill 2022).

Description of the intervention

Although it is standard practice to prescribe topical antimicrobial drops or ointments for corneal abrasions as prophylaxis against infection, there is variability in practice patterns for treatment of the pain (Hamill 2022; Sabri 1997). Ointments, bandage contact lenses, and patching of the eye closed under a gauze pad may decrease discomfort by reducing direct exposure of the defect and minimizing the mechanical irritation caused by repeated eyelid movement. It is theorized, however, that patching and bandage contact lenses could potentiate corneal infections by decreasing the cycling of tears over the ocular surface, thereby trapping microbes and impeding the action of host immune factors and antimicrobial medications (Hamill 2022). A Cochrane Review found that patching may not aid with healing or pain control. No conclusions, however, could be drawn about the relative risk of complications (Lim 2016). Bandage contact lenses are another modality for ameliorating pain through barrier coverage while allowing for blinking, normal cosmesis, and the ability to see. In the setting of ocular surface surgeries, such as corneal cross-linking or PRK, the placement of a bandage contact lens is standard practice. Although the clinical efficacy and safety of bandage contact lenses have been established to some degree in the setting of traumatic corneal abrasions (Menghini 2013; Vandorselaer 2001), it is well-known that extended contact lens wear increases the risk of infection and, therefore, contact lens use may be discouraged for corneal abrasions judged to be at high risk for microbial inoculation (Hamill 2022; Poggio 1989; Schein 1989).

In contrast to systemic analgesics such as oral acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), gabapentin, and opioids for abrasions, topical pharmacologic analgesics have the most direct, local effect on ocular pain with limited systemic side effects. Classes of topical ophthalmic treatments for corneal pain include NSAIDs (ketorolac, diclofenac, indomethacin, bromfenac, flurbiprofen, nepafenac) as well as amide and ester analgesics (tetracaine, proparacaine, lidocaine). Amide and ester anesthetics act to inhibit electrical conduction on axons by blocking sodium channels on the inner wall of the cell membrane (Levine 2017). The duration of action of these medications is approximately 20 to 30 minutes, and they therefore require frequent dosing for use in the outpatient setting to be effective (Levine 2017). Analgesic intervention may be administered as an adjuvant to other treatments for corneal analgesia including bandage contact lenses, ointments, patching, topical NSAIDs, or oral analgesics. Here we study the efficacy and safety of topical amide and ester anesthetics for corneal abrasions.

How the intervention might work

Topical ophthalmic amide and ester medications act directly on sensory corneal nerve endings to relieve pain. In the clinical setting, these medications provide immediate relief to ocular surface pain to permit a thorough eye exam. Likewise, the immediate

effectiveness of these medications also allows for excellent analgesia for a wide variety of ocular procedures (Levine 2017). These analgesic properties may be therapeutic over several days of outpatient use as a corneal epithelial defect heals. Accordingly, a recent systematic review found that topical NSAIDs for corneal abrasions significantly reduced pain and oral analgesia use without a difference in complications compared with control (Yu 2021).

Why it is important to do this review

Despite potential analgesic benefits from outpatient use of topical ophthalmic amides and esters, their use has become a topic of great controversy. Multiple published case reports and series have identified severe ocular complications associated with the outpatient use of topical anesthetic medications (Aksoy 2013; Ansari 2006; Ardjomand 2002; Chen 2004; Chern 1996; Dornic 1998; Epstein 1968; Katsimpris 2007; Khakshoor 2012; Kim 1997; Lee 2008; Pharmakakis 2002; Rosenwasser 1990; Varga 1997; Webber 1999; Willis 1970; Wu 2016; Yagci 2011). Reported complications include infection, corneal scarring, perforations, and severe ocular morbidities requiring evisceration or enucleation. In fact, topical anesthetic abuse seems to be a distinct entity with characteristic features such as persistent epithelial defects, corneal stromal ring infiltrates, disproportionate pain, and concurrent substance abuse disorder (Rosenwasser 1990). A person abusing one of these topical medications may have obtained it in a surreptitious way or may not admit to their use, making the diagnosis of abuse and treatment challenging. In support of these concerns, an intact corneal sensation from the trigeminal nerve is integral to the feedback loop that heals and maintains the ocular surface (Shaheen 2014). People with neurotrophic corneas (decreased or absent corneal sensation often from insults to the trigeminal nerve from herpes simplex virus, varicella-zoster virus, ocular surgery, neurosurgery, diabetes, or other causes) have chronically high rates of dry eye, non-healing epithelial defects, microbial keratitis, corneal scarring, corneal thinning, and corneal perforation (Chang 2022). Although the pain response to a corneal abrasion is severe, nociception is part of a protective sensory mechanism that includes increased tear production, the blink reflex, and the stimulation of growth factors important for healing (Chang 2022). The pain itself may serve as a harbinger of a complication, prompting timely presentation to medical care. In addition to interrupting the neural feedback loop, there is evidence that anesthetic medications may be directly cytotoxic to the corneal epithelium, although the full mechanism remains to be studied (Boljka 1994; Parsons 2022; Peyman 1994). Embracing many of these sentiments, a survey of 75 corneal specialists found universal opposition to the outpatient use of topical anesthetics (Lee 2019). However, there is a paucity of studies both designed and sufficiently powered to establish a causal relationship between outpatient topical anesthetic use and ocular complications. Although the collective body of case reports and series indicates a syndrome of topical anesthetic abuse (often with devastating consequences), it is unclear whether a strict prohibition is warranted, or whether these medications can be safely administered in a controlled and limited fashion in order to relieve suffering, in the same manner that topical steroids are prescribed for pain and inflammation despite potential for abuse and adverse events. Given the prevalence of both traumatic and surgically created corneal abrasions, an evidence-based analgesic strategy for corneal epithelial defects will have broad implications for clinical care. Our goal is to review outcome data from randomized controlled trials (RCTs) of topical amide and ester anesthetics for the efficacy of analgesia and safety for corneal epithelial defects resulting from both trauma and ocular surface surgery. Since particularly devastating complications may be rare, pooling data from multiple studies provides more statistical power to estimate the benefits and risks of use more accurately and precisely than any single RCT.

OBJECTIVES

To assess the effectiveness and safety of topical ophthalmic anesthetics compared with placebo or other treatments in persons with corneal abrasions.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) in this review. We included all eligible trials irrespective of their publication status. We planned to include within-person trials, where eyes had been allocated randomly to the intervention and comparator, but none were found.

Types of participants

We included trials that enrolled participants of all ages who had corneal abrasions within 48 hours of presentation, and from varying causes, including accidental trauma and ophthalmic surgery.

Types of interventions

We included trials that compared topical ophthalmic anesthetics (amide or ester class) with a non-amide or non-ester control group (either placebo, non-treatment, or alternative treatment). We also included trials in which topical anesthetics with an NSAID were compared with a control group (see Differences between protocol and review). We excluded trials in which participants were given topical anesthetics only once after trauma- or surgery-induced abrasion because of negligible clinical benefits or harms associated with the transient pharmacological effects of topical anesthetics.

Types of outcome measures

Primary outcomes

Critical outcomes

- Pain control: change in participant-reported ocular pain as measured using a pain scale that is continuous (e.g. 0 to 10 cm visual analog scale, VAS) or discrete (e.g. numerical rating scale 0 = "no pain" through 10 = "worst pain imaginable") from baseline to 24 hours, 48 hours, and 72 hours after treatment initiation. When the change scores were not available, we used pain scores measured at the above-mentioned follow-up time points.
- Epithelial healing: proportion of participants without complete resolution of epithelial defects by 24 to 72 hours.
- Complications: proportion of participants with adverse events (e.g. microbial keratitis or stromal infiltration, corneal stromal thinning, corneal perforation, surgical interventions) reported at the longest follow-up time of the study. Complications that suggest abuse would be nonhealing epithelial defect, stromal infiltration, thinning, or perforation. The last two would be seen most likely after more than a week of frequent use of topical anesthetic.

Secondary outcomes

Important outcomes

- Treatment failure: proportions of participants who required rescue oral analgesics by 72 hours after treatment initiation.
- Quality of life: mean changes in quality of life as measured by a validated instrument for health-related or vision-related quality of life, or functions of daily activity as quantified by the 7 or 12 Instrumental Activities of Daily Living checklist, as defined in the original study. We planned to use data from the longest follow-up time of the study. When the change scores were not available, we planned to use mean scores instead.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist searched the following electronic databases for potentially eligible RCTs and controlled clinical trials. There were no restrictions based on language or year of publication. The search was performed on 19 February 2022 and updated on 10 February 2023. Search details are provided in the specified appendices.

- Cochrane Central Register of Controlled Trials (CENTRAL, which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (2023, Issue 2) (Appendix 1).
- MEDLINE Ovid (All) (1946 to 10 February 2023) (Appendix 2).
- Embase.com (Elsevier) (1947 to 10 February 2023) (Appendix 3).
- PubMed (1948 to 10 February 2023) (Appendix 4).
- Latin American and Caribbean Health Sciences Literature Database (LILACS) (1982 to 10 February 2023) (Appendix 5).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) (Appendix 6).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp) (Appendix 7).

Searching other resources

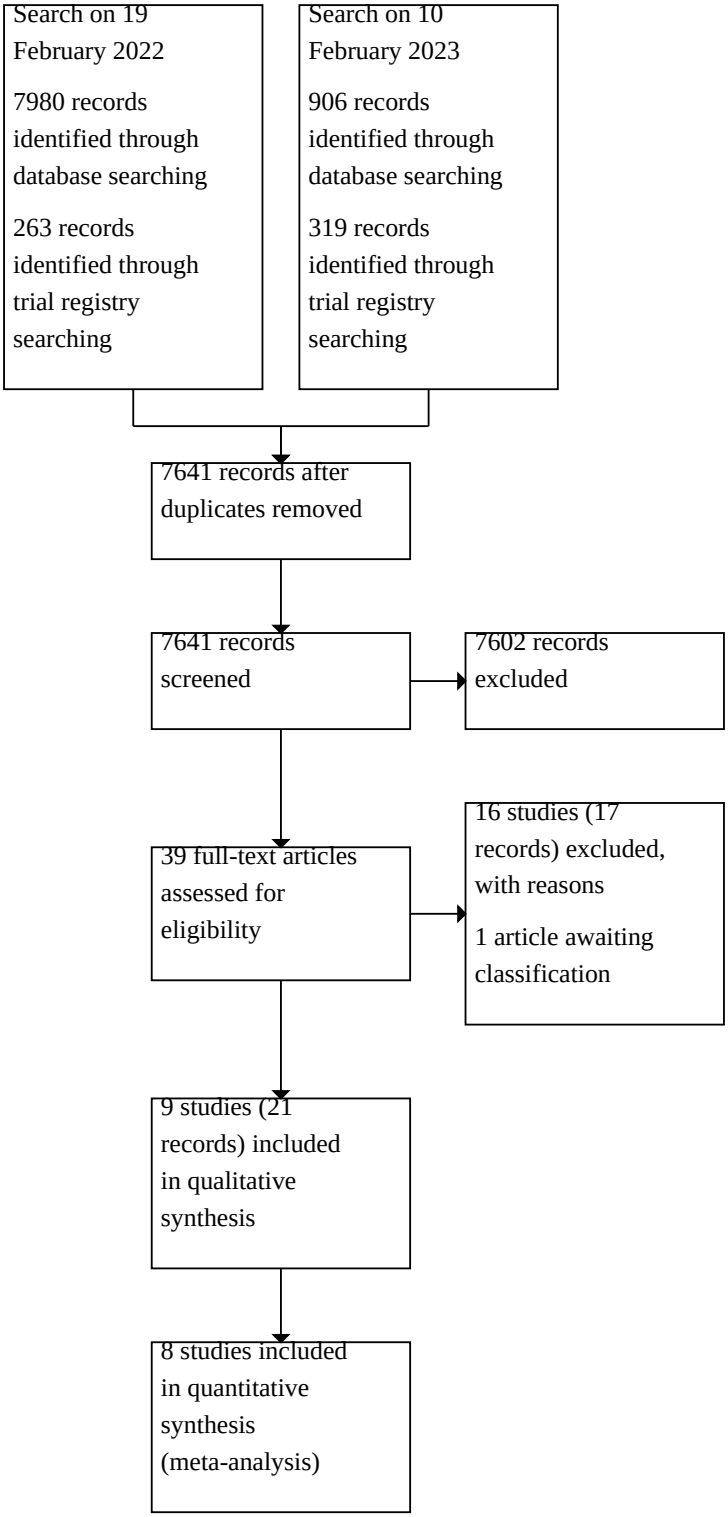
We searched the reference lists of studies that were included following full-text screening. We also searched the reference lists of systematic reviews and guidelines for additional trials missed by the electronic searches. We did not handsearch specific journals or conference proceedings as many eyes and vision conferences are included in Embase.

Data collection and analysis

Selection of studies

The Information Specialist performed electronic searches of the selected databases and removed duplicates. We worked in pairs (MS, KC, CI, SL, LL, IK) and independently screened the titles and abstracts resulting from the searches using the web-based software Covidence. We resolved disagreements by discussion. We noted the number of citations considered not relevant in the selection of studies flow diagram (Figure 1). We obtained full-text copies of reports from trials judged to be potentially relevant by either review author. We corresponded with study investigators to clarify study eligibility, as appropriate. For trial registration records and meeting abstracts with no full-text report, we contacted the study investigators for desired information about study methods and any outcome data that were available. Whenever study investigators did not respond within two weeks, we proceeded with the information available.

Figure 1. Study flow diagram



Working in pairs, review authors (MS, KC, CI, SL, LL, IK) independently assessed the full-text copies of reports for inclusion by applying the Criteria for considering studies for this review. We resolved disagreements by discussion. For non-English study reports, we used Google Translate for the initial translation of the Methods and Results sections of the report, which was sufficient to determine eligibility; we therefore did not enlist human translation. We were not masked to the names of the authors, institutions, or journal publications.

We listed all studies excluded during full-text screening and provided a justification for exclusion (see Characteristics of excluded studies).

Data extraction and management

We piloted the data extraction form developed by Cochrane Eyes and Vision (CEV) in Covidence. We worked in pairs of review authors (MS, KC, CI, SL, LL, IK) to independently extract data. We resolved discrepancies through discussion.

We contacted trial investigators for desired data that had not been reported and allowed two weeks for a response before proceeding with the available data. All data were imported directly into RevMan Web by one author (LL) and one author (SL) verified the accuracy of the data imported.

For multi-arm studies, we used data relevant to our intervention and comparator groups, taking care not to double-count or omit participants. We planned, when two randomly allocated trial arms (interventions or comparators) contained relevant data, to combine data from them using the calculator within RevMan Web. Where data transformation was required (e.g. standard errors (SEs) from standard deviations (SDs), extracting data presented only in graphs or figures) we followed the guidance outlined in Chapter 5 and Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022a; Li 2022). We extracted data available only in graphs or figures using browser-based data extraction software (WebPlotDigitizer).

Assessment of risk of bias in included studies

We assessed the potential risk of bias in each included study using Cochrane's RoB 2 tool, as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022b). Working in pairs, review authors (MS, KC, CI, SL, LL, IK) assessed the risk of bias independently using the RoB 2 Excel tool (22 August 2019 version for individually randomized, parallel-group trials; available from riskofbiasinfo.org). We compared judgments and resolved disagreements by discussion. We assessed bias for the 'intention-to-treat effect' for the efficacy outcome of pain control by 48 hours and the safety outcome of complications at the longest follow-up time.

We considered and assessed risk of bias in the following domains:

- bias due to the randomization process;
- bias due to deviations from the intended intervention;
- bias due to missing outcome data;
- bias in measurement of the outcome; and
- bias in selection of the reported result.

Based on these five domains, we assigned an overall risk of bias judgment of 'high', 'some concerns', or 'low' risk of bias.

Measures of treatment effect

We referred to the guidance outlined in Chapters 9 and 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022; McKenzie 2022). We calculated the risk ratio (RR) and 95% confidence intervals (95% CIs) for dichotomous outcomes (proportion of participants without full epithelial healing at 24 to 72 hours). We calculated the risk difference (RD) and 95% CI for dichotomous outcomes when one or more trials had zero events in both arms. We calculated the mean difference (MD) and 95% CIs for continuous outcomes (changes in pain scores from baseline to 24, 48, and 72 hours after treatment; risk of adverse events at longest time point). We had planned to calculate the standardized mean difference (SMD) and 95% CIs for continuous outcomes measured using different scales (e.g. mean change in quality of life or activities of daily living). Where possible, we checked for the skewness of continuous data (Altman 1996).

Unit of analysis issues

Where variations on RCTs were included, we referred to Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021c). When both eyes of participants had been allocated to the same or different interventions, we extracted the results that accounted for the correlation between eyes. Whenever the investigators of a primary study had failed to consider the correlation between two eyes, or it was unclear whether they had, we excluded those studies in the sensitivity analysis.

Dealing with missing data

We requested missing data from study authors and allowed two weeks for a response before proceeding with the available data. We calculated missing standard deviations using P values, based on the methods outlined in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022a). We did not impute missing data ourselves. When outcome data based on intention-to-treat (ITT) analysis were not available, we collected and combined, whenever feasible, data as reported by authors of the included trials based on either per-protocol or complete-case analysis. Either approach assumed that some outcome data were missing at random; we assessed whether this assumption was reasonable by collecting data from each included trial on the number of participants excluded or lost to follow-up and reasons for loss to follow-up by treatment group when reported. This information was also used to assess potential risk of bias in individual trials (Higgins 2022b).

Assessment of heterogeneity

We examined the overall characteristics of the studies and participants (see Characteristics of included studies); in particular, we looked at the type of participants and types of interventions, to assess the extent to which the studies were similar enough to make pooling study results in meta-analyses sensible.

We examined the forest plots of study results for consistency of effect estimates from individual studies; in particular, we considered the size and direction of effects and overlap of confidence intervals. We calculated the I^2 statistic, which is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) (Higgins 2002). We considered I^2 values over 75% to indicate considerable heterogeneity but also considered Chi^2 and P values (Deeks 2022).

Assessment of reporting biases

We planned that, when there were 10 trials or more included in a meta-analysis, we would construct funnel plots and consider tests for asymmetry to assess small study effects, which may be due to publication bias and other factors, according to Chapter 13 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Page 2022). Because there were only nine included trials that varied in the interventions and outcomes reported, we did not construct funnel plots. We examined selective reporting of results during the assessment of potential risk of bias.

Data synthesis

We referred to Chapters 9 and 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* for data synthesis (Deeks 2022; McKenzie 2022). We pooled data using random-effects models in RevMan Web when there were three or more trials reported on the same outcome. When data were sparse (fewer than three trials), we used a fixed-effect model for meta-analysis of outcomes.

Whenever there was substantial heterogeneity among individual study effect estimates, such that a combined result may not provide a good summary of the individual trial results, we did not pool the data but described the pattern of the individual study results. When there was evidence of statistical heterogeneity but all the effect estimates were in the same direction, such that a combined estimate would seem to provide a good summary of the individual trial results, we combined the data.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analysis if there were more than 10 trials (Sulewski 2022). Although only nine trials were included, we performed subgroup analysis on 'pain control', 'epithelial healing', or both, by the following covariates:

- etiology of corneal abrasion: ocular surgery or trauma;
- exposure to intervention medications:
  - duration of use (24 to 48 hours versus 48 hours or longer);
  - concentration of anesthetic (diluted versus standard concentration).

We were unable to analyze outcomes by gender or race as there were minimal demographic data in the study reports and no outcomes reported by treatment arm within the demographic subgroups. We did not perform subgroup analysis by frequency of use because all included trials had a frequency of use ≥ 4 times per day (see Differences between protocol and review).

Sensitivity analysis

We performed sensitivity analysis by:

- excluding studies judged to be at an overall high risk of bias;
- excluding within-person studies that had not addressed the correlation of outcomes in pairs of eyes when reporting the trial results.

Summary of findings and assessment of the certainty of the evidence

We prepared summary of findings tables to present relative and absolute risks estimated from the included studies based on interventions compared (Schünemann 2022). Working in pairs, review authors (MS, KC, CI, SL, LL, IK) independently graded the overall certainty of the evidence, resolving discrepancies by discussion, for the following efficacy and safety outcomes using the GRADE classification (Schünemann 2022):

- Efficacy outcomes: changes in mean participant-reported ocular pain from baseline to 24 hours, 48 hours, and 72 hours after treatment initiation.
- Safety outcomes:
  - proportion of participants without complete resolution of epithelial defects by 24 to 72 hours;
  - proportion of participants with adverse events reported at the longest follow-up time of the study.

We considered the following five elements when deciding to downgrade the certainty of the body of evidence from a high to a low level:

- high risk of bias among included studies;
- indirectness of evidence;
- unexplained heterogeneity or inconsistency of results;
- imprecision of results; or
- high likelihood of publication bias.

We applied study-level risk of bias assessments, based on responses to signaling questions in domains 1 to 3 of the RoB 2 tool, to provide judgment on risk of bias when we graded outcomes that we did not choose for complete RoB 2 assessment.

RESULTS

Description of studies

Results of the search

The Information Specialist found 7980 records in the electronic databases and 263 records in trial registries on 19 February 2022. The search was run again on 10 February 2023, which retrieved a further 906 records from electronic databases (date limit January 2022 to 10 February 2023) and 319 records from trial registries. We did not identify any eligible studies through supplemental searches. After removing duplicates, we screened 7641 records from which we excluded 7602 records. We then assessed 39 full-text articles for eligibility and included nine trials (21 records) in the current review (Figure 1). We labeled one study (Aseff 1997) as 'awaiting classification' because of incomplete data reported in the meeting abstract. We excluded 16 studies (17 records) and listed the reason for exclusion in the Characteristics of excluded studies.

Included studies

Types of trials

We give details of the nine included RCTs in the Characteristics of included studies table and summarize them in Table 1. The trials span the years 1994 to 2021, and they were conducted in multiple settings and locations. The median study length was seven days (interquartile range (IQR) 7 to 14 days; nine RCTs). The median study length was 11 days (IQR 7 to 18 days; 4 RCTs) for post-trauma trials and seven days (IQR 3 to 7 days; 5 RCTs) for post-surgical trials. The median anesthetic treatment duration was 24 hours (IQR 24 to 168 hours; nine RCTs). The median treatment duration was 36 hours (IQR 24 to 78 hours; four RCTs) for post-trauma trials and 24 hours (IQR 24 to 168 hours; five RCTs) for post-surgical trials.

Of the nine RCTs, four (44%) were conducted in the emergency department setting; three of these were single-center trials conducted in New Zealand (Waldman 2014), Australia (Ting 2009), and the United States (Shipman 2021). Ball 2010 included two tertiary care emergency departments in Canada. Five RCTs (56%) were in ophthalmology surgical settings; Shahinian 1997 had two study sites, one in Canada and in the United States, while the other four RCTs were single-center trials based in the United Kingdom (Verma 1995), Turkey (Oksuz 2006), France (Montard 1999), and South Korea (Lim 1999). Except for Oksuz 2006, which enrolled participants following pterygium surgery, all surgical trials enrolled patients who were status post photorefractive keratectomy (PRK).

The reporting of funding/sponsors varied; five trials did not have a statement regarding study funding, one reported there was no funding (Waldman 2014), and two stated partial support for authors from a foundation (Shipman 2021; Verma 1995). None of the trials reported industry funding. Five trials reported no conflict of interest among trial investigators; the author of one trial was a patent holder for the intervention (Shahinian 1997), and reports from the other trials did not include a disclosure statement.

All nine included trials had parallel-group designs. Eight RCTs had two treatment arms, while Lim 1999 had seven. Eight trials randomized participants to treatment and analyzed data from one study eye. Shahinian 1997 randomized post-PRK participants to treatments (N = 34); some participants had both eyes enrolled as study eyes, whereas others had a single study eye (N = 48 eyes). Four trials reported an a priori power calculation for the primary outcome of the trial; one stated the sample size for statistical significance without further detail (Verma 1995), and the remaining four trials did not state whether sample size calculations had been performed. Additionally, Waldman 2014 reported the power calculation for a secondary outcome. Four trials had associated trial registration records, one had been prospectively registered (Ting 2009), and three had been registered after the specified start date of participant enrollment (Ball 2010; Shipman 2021; Waldman 2014).

Types of participants

The nine included trials enrolled a total of 626 participants. Three of the seven treatment arms, one comparison and two separate interventions, of Lim 1999 were eligible for inclusion in this review (45/105 participants). We included in this review a total of 556 participants, with a median number of 45 participants per study (IQR 44 to 74).

Five trials described 242 participants (256 eyes) with post-surgical corneal defects: four from PRK (Lim 1999; Montard 1999; Shahinian 1997; Verma 1995) and one from pterygium surgery (Oksuz 2006). Four trials analyzed abrasions of traumatic etiology in a total of 314 participants (314 eyes) (Ball 2010; Shipman 2021; Ting 2009; Waldman 2014). The majority of abrasions involved corneal foreign bodies (47%, 148 eyes) or direct trauma (19%, 61 eyes).

One eye of each participant had been treated and followed except in one trial, in which both eyes were allocated to the same treatment for four participants (eight eyes) who had bilateral surgery on the same day (Shahinian 1997). It is unclear whether this method of assignment was used for second eyes of participants who had sequential surgery on separate days.

Baseline characteristics of participants varied by age, gender, and ethnicity. One trial did not report the gender of the participants (Shahinian 1997). Three of the eight trials that reported the participant gender reported numbers in the overall trial but not within individual treatment groups (Lim 1999; Montard 1999; Verma 1995). For example, Lim 1999 reported that 71% of trial participants were women (75/105) but did not report gender by treatment arm. Among these eight trials, a higher proportion of women was seen in trials that had examined iatrogenic corneal abrasions from refractive or pterygium surgery (60%, 166/278; four RCTs) compared with trials of participants seen in emergency departments for corneal abrasions (21%, 65/314; four RCTs).

None of the trials reported racial demographics. One trial conducted in New Zealand reported ethnicity of participants, with 59% (69/116) 'European', 7% (8/116) 'Maori', 2% (2/116) 'Other', and 32% (37/116) 'Not Reported' (Waldman 2014).

One trial did not report the age of participants (Shahinian 1997). Of the eight trials that had reported participants' ages at baseline, all participants were 18 years or older with one exception: Waldman 2014 enrolled one 17-year-old participant. Waldman 2014 also had the widest age range (17 to 74 years old). Seven trials reported either a mean or median age for participants, ranging from 27.8 to 47.9 years old.

Types of interventions

The nine included trials evaluated three of the commonly used topical anesthetics, of which types and concentrations varied: proparacaine (Ball 2010; Lim 1999; Shahinian 1997), tetracaine (Montard 1999; Shipman 2021; Ting 2009; Verma 1995; Waldman 2014), and lidocaine (Oksuz 2006). One study tested the amide anesthetic lidocaine 2% (Oksuz 2006). Two ester anesthetics of various concentrations were tested in the other trials: tetracaine (Montard 1999; Verma 1995; Waldman 2014 at 1%; Shipman 2021 at 0.5%; Ting 2009 at 0.4%) and proparacaine diluted from commercially available 0.5% to 0.05% (Ball 2010; Lim 1999; Shahinian 1997). Lim 1999 was a multi-arm trial that tested both proparacaine 0.05% alone and its combination with topical diclofenac 0.1%.

Four trials enrolled post-trauma patients who were sent home from the emergency department with topical anesthetics of varying concentration, frequency, duration, and total amount dispensed for self-administration (Ball 2010; Shipman 2021; Ting 2009; Waldman 2014). In Waldman 2014, investigators prescribed tetracaine 1%, dosed as often as every 30 minutes for 24 hours (1.5 mL total volume dispensed). In Shipman 2021, they prescribed tetracaine 0.5%, one drop every 30 minutes as needed for 24 hours (2 mL total volume dispensed). In Ting 2009, they prescribed tetracaine 0.4%, one drop every hour as needed for 48 hours (1.5 mL total volume dispensed). In Ball 2010, they prescribed proparacaine 0.05%, two to four drops as needed for seven days (40 mL total volume dispensed). The authors stated no minimum time interval between doses "allowing patients unlimited use of the study drug" (Ball 2010).

The other five trials enrolled patients following ophthalmic surgery that had caused a corneal epithelial defect (Lim 1999; Montard 1999; Oksuz 2006; Shahinian 1997; Verma 1995). In Oksuz 2006, starting one hour after pterygium surgery, participants were administered lidocaine 2% hydrochloride gel, 1 mL every hour

for three hours prior to hospital discharge. In Shahinian 1997, surgeons prescribed proparacaine 0.05%, one drop four times per day. In Verma 1995, they prescribed tetracaine 1%, one drop every 30 minutes "during waking hours" for 24 hours (40 drops total dispensed). In Montard 1999, they prescribed tetracaine 1%, every 30 minutes for 24 hours. In Lim 1999, they prescribed one group proparacaine 0.05%, one drop every four hours for seven days. The same dosing was used for the diclofenac 0.1% plus proparacaine 0.05% (Lim 1999).

Eight of the included trials compared topical anesthetics to placebo treatment, which included saline (Ting 2009; Verma 1995; Waldman 2014), artificial tears (Lim 1999; Oksuz 2006; Shahinian 1997; Shipman 2021), and a "colour- and smell-matched" placebo, likely vehicle (Ball 2010). The only trial that used an active comparator was Montard 1999, in which the investigators compared tetracaine 1% with topical diclofenac 0.1%. Among the four trials that enrolled post-trauma patients (Ball 2010; Shipman 2021; Ting 2009; Waldman 2014), Shipman 2021 was the only trial that had used artificial tears whereas the other three trials used saline as the comparator. In contrast, among the four trials that enrolled post-surgical patients (Lim 1999; Montard 1999; Oksuz 2006; Shahinian 1997; Verma 1995), Verma 1995 was the only trial that used "physiologic saline" as the comparator. The other three trials used other brands of artificial tears; in Oksuz 2006 artificial tears in gel form were used. In all included trials, these placebo treatments were prescribed at the same frequency and duration as the respective study's topical anesthetic treatment arm. The only trial with different frequency and duration between treatment arms was Montard 1999, in which investigators prescribed tetracaine 1% every 30 minutes for 24 hours but allowed diclofenac 0.1% to be instilled every four hours for three days.

Oral analgesics were prescribed in all but one trial (Oksuz 2006). In two trials, oral analgesics were dosed on a schedule: two tablets of co-proxamol (dextropropoxyphene 32.5 mg and paracetamol 325 mg) every eight hours for two days (Verma 1995) and two tablets of 500 mg paracetamol at 08:00, 12:00, 16:00, and 20:00 over 24 hours (Waldman 2014). Six of the RCTs prescribed various analgesics on an 'as-needed' basis for breakthrough pain, including paracetamol-noramidopyrine (Montard 1999), acetaminophen and codeine (Ball 2010), acetaminophen and hydrocodone (Shahinian 1997; Shipman 2021), and mefenamic acid (Lim 1999); one study did not specify the analgesic (Ting 2009).

The five surgical trials had different pre-, peri-, and postoperative protocols (see Characteristics of included studies for details). In two trials, bandage contact lenses were placed in post-surgical eyes (Lim 1999; Shahinian 1997). All surgical eyes had occlusive patching in Oksuz 2006. Topical antibiotics were used in all RCTs except for Oksuz 2006. A variety of antibiotics were prescribed: chloramphenicol 0.5% (Verma 1995), chloramphenicol 1% (Waldman 2014), ofloxacin 0.3% (Montard 1999), and unspecified concentrations of ofloxacin (Lim 1999), polymyxin B sulfate/trimethoprim sulfate (Shipman 2021), and gatifloxacin (Ball 2010). One study used a combination of 0.3% tobramycin and 0.1% dexamethasone (Shahinian 1997). Antibiotics were not prescribed equally within and between groups in one study; 8/22 participants in the tetracaine group and 8/18 in the saline group received antibiotics (Ting 2009).

Critical outcomes

Pain control from baseline to 24 hours, 48 hours, and 72 hours after treatment initiation

All included nine trials assessed pain intensity using pain scoring systems where higher numbers represented higher pain intensity. Eight trials used a VAS, with two using 0- to 100-point continuous scales (Ting 2009; Waldman 2014) and the others using a 0- to 10-point continuous scales. Shahinian 1997 used a 0- to 10-point continuous pain intensity scale but did not specify whether the instrument was a visual analog or numeric scale.

Baseline pain was recorded in two of the four trials of participants with traumatic corneal injuries (Shipman 2021; Waldman 2014). Some participants reported no pain at baseline and were analyzed in a mixed-model to account for multiple measurements (Waldman 2014). Ting 2009 did not report baseline pain and Ball 2010 only reported the change score. In post-surgical trials, the baseline pain following surgery was not reported. Shahinian 1997 only reported the mean pain before taking study drops. The earliest time point at which postoperative pain was reported was one hour (Montard 1999), four hours (Oksuz 2006), or the end of the day (Lim 1999). In Verma 1995, the baseline pain could not be extracted from the presented figure.

A clinically important difference in the VAS measurement of pain intensity was defined in three trials: 16 mm (SD 25 mm) on a 100 mm VAS (Waldman 2014), 2 cm (SD 2 cm) on a 10 cm VAS (Ball 2010), and 1.5 cm (SD 2.5 cm) on a 10 cm VAS (Shipman 2021). Waldman 2014 cited two observational studies that had validated the use of the VAS to assess acute (primarily abdominal) pain in the emergency department setting as the basis for selecting 16 mm. Ball 2010 used an informal survey of attending emergency department physicians. Shipman 2021 did not report how 1.5 cm was selected as a clinically important difference. Verma 1995 defined 3 cm as an acceptable level of pain on a 10 cm VAS but did not specify how this number was chosen.

We included data from six trials for pain outcomes reported at up to 24, 48, and 72 hours. Lim 1999 reported the mean pain intensity and P values comparing artificial tears versus anesthetic groups on day one but not on days two and three. We used the P value to determine the standard deviation for day one in order to include the data at 24 hours following the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022a). Oksuz 2006 reported pain scores at four, seven, and 10 hours postoperatively, but we included only the 10-hour follow-up value in the analysis of pain control from baseline to 24 hours. Montard 1999 reported the pain profile at 24 hours based on a single factor analysis to extrapolate pain during sleeping hours.

The mean and standard error were extracted from figures for 24-, 48-, and 64-hour time points reported in Verma 1995. Waldman 2014 used a mixed-model to account for multiple measurements over the 48 hours and separately reported the mean difference for follow-up durations of 24 and 48 hours. Shipman 2021 recorded the change in scores from pre- and two minutes post-instillation of study drops and reported the overall pain rating at 24 to 48 hours follow-up.

We did not include pain score data from three trials in the meta-analysis (Ball 2010; Shahinian 1997; Ting 2009), because the timeframe of the trial results was outside the pre-specified time

windows or the trial results were reported as period averages. The authors of Shahinian 1997 reported averaged pain scores over the first postoperative week as documented by participants immediately before and one minute after applying the study eye drops (used as needed). Similarly, Ball 2010 reported the aggregated median change scores from all recorded pre- and five minutes post-use of study drops over seven days. Ting 2009 reported the total pain burden over 36 hours.

Epithelial healing by 24 to 72 hours

Epithelial healing was assessed by slit lamp biomicroscopy in the majority of trials (67%; 6/9) (Lim 1999; Oksuz 2006; Shahinian 1997; Shipman 2021; Ting 2009; Waldman 2014); two other trials used digitized and computer-assisted measurements (Montard 1999; Verma 1995). One trial stated only that "the ophthalmologist was directed to identify signs of delayed wound healing" (Ball 2010). Despite the variations in measurements of epithelial healing performed among the trials, we were not able to use all reported data in our analysis of this outcome. Three trials reported mean time to epithelial healing, but proportions of eyes with epithelial healing at 24 to 72 hours could not be derived (Montard 1999; Oksuz 2006; Shahinian 1997). Ball 2010 assessed eyes at three, five, and seven days after injury and reported, "no ocular complications or evidence of delayed wound healing in either group."

Complications reported at the longest follow-up time

The median study length of seven days (post-surgical trials) and 11 days (post-trauma trials) gives an indication of the longest follow-up. Methods of assessing complications included clinical assessment, such as slit lamp biomicroscopy, by an ophthalmologist or emergency medicine physician (Verma 1995; Waldman 2014). Other methods of assessing complications included the following: eliciting complaints from participants using a list of qualifying complications (Shipman 2021; Waldman 2014), eliciting complaints from participants without a list, judgment by an ophthalmologist who was asked to identify complications including any that appeared to be related to the initial injury or the use of study medications (Ball 2010), or no report of method used (Montard 1999). These subjective assessments were conducted at the time of clinical assessment, during telephone interview (Ball 2010; Shipman 2021; Waldman 2014), or in response to text messages (Waldman 2014). Most trials did not provide details on complications such as microbial keratitis or stromal infiltration, corneal stromal thinning, corneal perforation, or surgical interventions. Four trials reported specific adverse events (Shipman 2021; Ting 2009; Verma 1995; Waldman 2014). Three other trials stated only that there had been no adverse events (Ball 2010; Lim 1999; Oksuz 2006). The remaining two trials provided no information about complications (Montard 1999; Shahinian 1997).

Important outcomes

Treatment failure at 72 hours after treatment initiation

Investigators of one study reported the number of eyes that had required analgesia for breakthrough pain, from 24 hours to two weeks (Ting 2009). Reports from no other trial provided data for this outcome because our protocol specified the proportion of participants (or eyes) that were treatment failures rather than the amount of analgesia taken over the study period (e.g. median number of hydrocodone tablets over 48 hours). In addition, one indication of treatment failure as defined by our protocol was the use of rescue oral analgesics for pain not alleviated by topical anesthetic medication. Therefore, trials in which oral analgesics were prescribed to prevent breakthrough pain were not included in the analysis (Verma 1995; Waldman 2014).

Oksuz 2006 did not describe the use of oral analgesics. Lim 1999 assessed the number of oral analgesics used but did not report the results. Four of the included trials reported the amount of oral analgesia taken over the study period as a continuous measure, so we did not include these in the analysis (Ball 2010; Montard 1999; Shahinian 1997; Shipman 2021).

Quality of life

None of the included trials assessed health-related, vision-related, or function-related quality of life outcome assessments.

Excluded studies

We documented reasons for exclusion of 16 studies in the table of Characteristics of excluded studies. We translated five non-English articles using Google Translate; the original languages were French (Henrotte 1972), Portuguese (Ferreira 1992), Italian (Filippone 1967), and German (Steiner 1966; Weindler 2001). Further translation was not required to determine whether the trial was eligible for inclusion. We contacted the investigators of two trials that had registration records to inquire about trial status and data availability; one confirmed the trial had been halted, and data were not available (NCT02483897); the other investigator stated that the trial had never been initiated and had never enrolled participants (NCT02771392). For another study, we requested information regarding randomization but did not receive any response (Cherry 1996). Based on other published reports referenced in Cherry 1996, we determined that the study did not meet our eligibility criteria. Of the 16 excluded studies, eight were excluded for ineligible populations, four were excluded for ineligible study designs, three had ineligible interventions, and one had an ineligible comparison group.

Studies awaiting classification

We did not have enough information to confidently include or exclude a study reported only in a meeting abstract (Aseff 1997). Multiple contact attempts for all listed authors of the abstract were unsuccessful.

Risk of bias in included studies

We assessed the risk of bias for two outcomes: 1) the mean participant-reported ocular pain from baseline to 48 hours (Figure 2), and 2) the proportion of participants with complications (Figure 3). We assessed the risk of bias in two trials that reported the first outcome (Shipman 2021; Verma 1995), and seven trials for the second outcome (Ball 2010; Lim 1999; Oksuz 2006; Shipman 2021; Ting 2009; Verma 1995; Waldman 2014). For the domain-specific judgments, the domains for which we assessed trials to be at the highest risk of bias were missing outcome data or selective reporting of outcome data.

Figure 2. Risk of bias: Change in participant-reported ocular pain from baseline to 48 hours

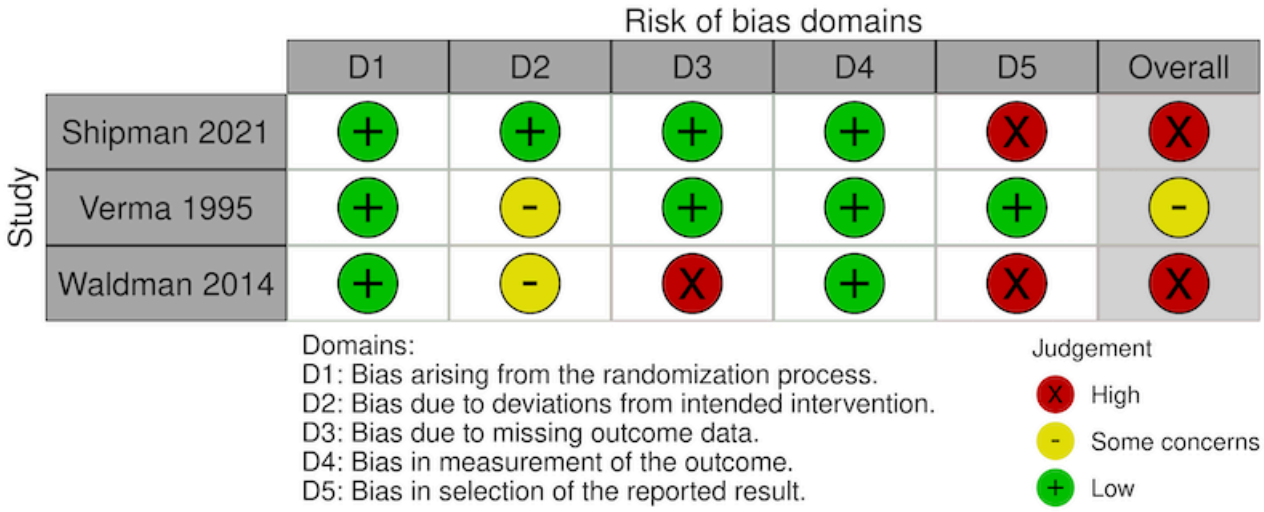
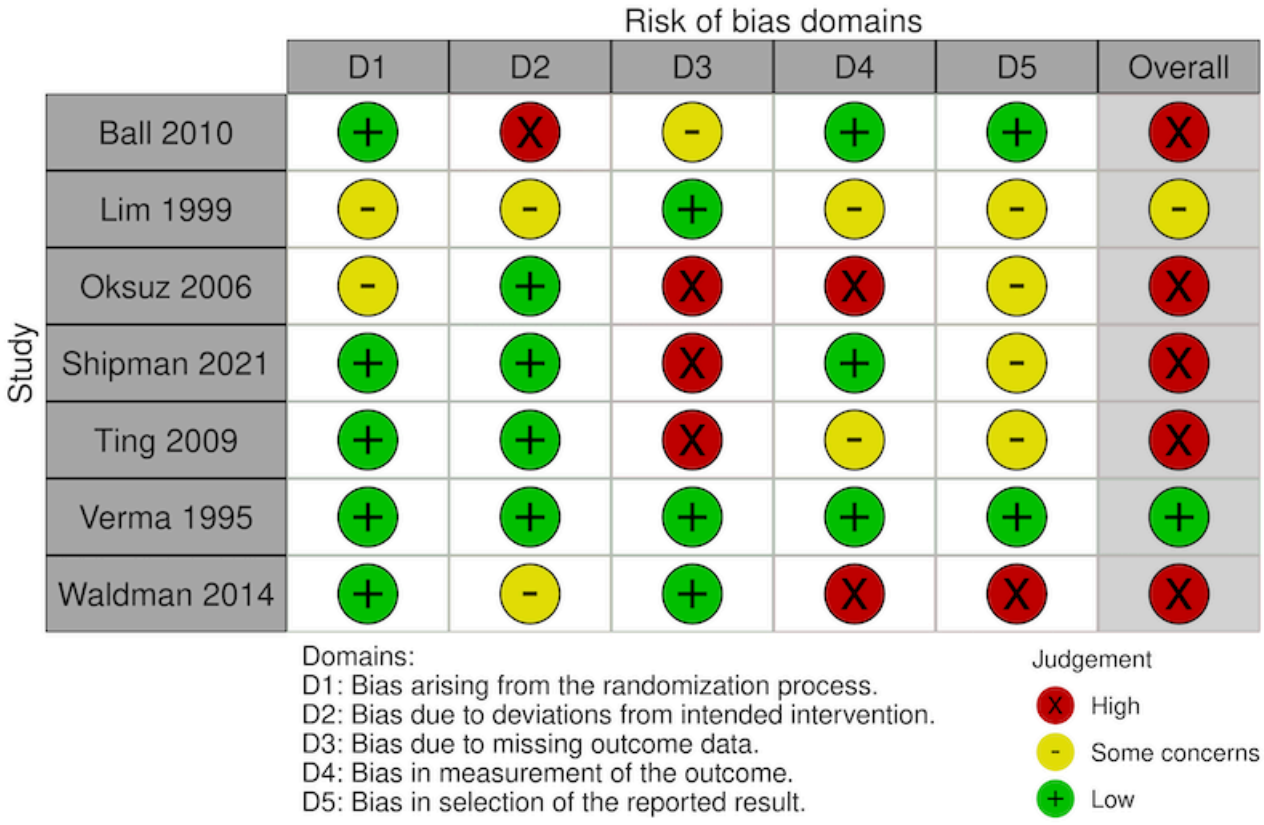


Figure 3. Risk of bias: Proportion of participants with complications at longest time point



Domain 1 - Bias arising from the randomization process

We judged five trials to have low risk of bias as they described methods of randomized sequence generation and methods to conceal allocation, such as the use of sealed, opaque envelopes (Shipman 2021) and "research pharmacists not involved in the design or conduct of the study prepared identical, clear, minim packs" (Ting 2009). Neither Lim 1999 nor Oksuz 2006 described a method of allocation concealment, and few baseline characteristics of participants were provided. Therefore, we had some concerns about risk of bias for this domain.

Domain 2 - Bias arising from deviations from intended interventions

Two trials addressed the primary outcome of pain at 48 hours (Shipman 2021; Verma 1995). We assessed one study as possessing low risk of bias because of deviations from intention-to-treat (Shipman 2021). For Verma 1995, we had some concerns about bias.

For adverse events, we assessed the evidence from four trials as indicating low risk of bias arising from deviations from intended interventions (Oksuz 2006; Shipman 2021; Ting 2009; Verma 1995). We had some concerns about two trials because of unclear post-randomization exclusion of participants (Waldman 2014), no mention of adverse events (Lim 1999), and the potential unmasking of participants due to the burning sensation of tetracaine (Waldman 2014). We judged one study to have a high risk of bias because data were excluded for avoidable reasons, such as not having medication, not recording pain measurements, and loss to follow-up (Ball 2010).

Domain 3 - Bias due to missing outcome data

Regarding pain control by 48 hours, we judged one study as having a low risk of bias because of few missing outcome data (Shipman 2021), and one study as having high risk of bias because of differences in follow-up rates between treatment groups (Verma 1995).

For adverse events at the longest follow-up, we assessed three trials as having low risk of bias due to no missing data (Lim 1999; Waldman 2014; Verma 1995). We had some concerns about bias in one study because 20% of participants did not contribute adverse event data and the investigators did not provide any explanation (Ball 2010). We assessed three trials as possessing a high risk of bias because not all participants were required to follow up after 24 hours (Oksuz 2006), or had multiple follow-up visits with varying attendance, and self-reporting of adverse event data (Shipman 2021; Ting 2009). There was substantial loss to follow-up for the clinical assessment at the 48-hour (Waldman 2014) and one-week (Shipman 2021) time points. In Waldman 2014, all participants who missed clinic follow-up were successfully contacted by other methods (telephone, text messaging). In Shipman 2021, there was still missing data for 32% of participants after similar use of text messaging.

Domain 4 - Bias in outcome measurement

For pain control by 48 hours, we assessed two included trials as having low risk of bias associated with measurement of the outcome (Shipman 2021; Verma 1995).

For collection of adverse events, we judged three trials as possessing low risk of bias (Ball 2010; Shipman 2021; Verma 1995). In two trials, there were some concerns about bias arising from examiners not being masked to treatment and sparse detail(s) of how adverse events were evaluated (Lim 1999; Ting 2009). We assessed two trials as having a high risk of bias for reasons such as disparity in the frequency of scheduled clinical assessments. In one study, delayed healing increased the frequency of assessment only for patients with incomplete healing (Oksuz 2006). In the second study, the baseline and follow-up assessments in the emergency department were not described in detail, for example by gross physical exam, slit lamp biomicroscopy, or fluorescein dye uptake as visualized by under cobalt blue light, and relied on self-reporting of adverse events (which may have gone undetected in the anesthetic group) (Waldman 2014).

Domain 5 - Bias in selective reporting of outcome data

Concerning pain control by 48 hours, we assessed one study as having low risk of bias because all outcomes were reported (Verma 1995), and another study as having high risk of bias because reporting of results diverged from the statistical plan in the protocol (Shipman 2021).

For bias related to reporting adverse outcomes, we deemed two trials to have low risk of bias (Ball 2010; Verma 1995). We had some concerns about bias in four trials due to no study protocol being found or no definition of an adverse event (Lim 1999; Oksuz 2006; Ting 2009), multiple possible time points of measurement (Oksuz 2006), no data analysis plan, and multiple possible definitions used across the study (Shipman 2021). We considered one study at high risk of bias due to having no statistical analysis plan, a large cohort of participants excluded in a post hoc fashion for an unexpected result (i.e. persistent rust rings), and multiple time points with different numbers of participants at each (Waldman 2014).

Overall assessment of bias

In summary, for the outcome of pain control at 48 hours, we deemed one study to be at high risk of bias (Shipman 2021), and another study to raise some concerns about risk of bias (Verma 1995). For the outcome of adverse events at the last follow-up time point, we judged one of the trials to be at low risk of bias, we had some concerns about risk of bias in one study, and we judged the remaining five trials to have high risk of bias.

Effects of interventions

See: **Summary of findings 1** Topical ophthalmic anesthetic compared with placebo or NSAID; **Summary of findings 2** Topical ophthalmic anesthetic plus NSAID compared with placebo

We reported the effects of topical anesthetics in the following two comparisons: Comparison 1: Anesthetics alone versus placebo or NSAID (Summary of findings 1); Comparison 2: Anesthetics plus NSAID versus placebo (Summary of findings 2).

Comparison 1: Anesthetics versus placebo or NSAID

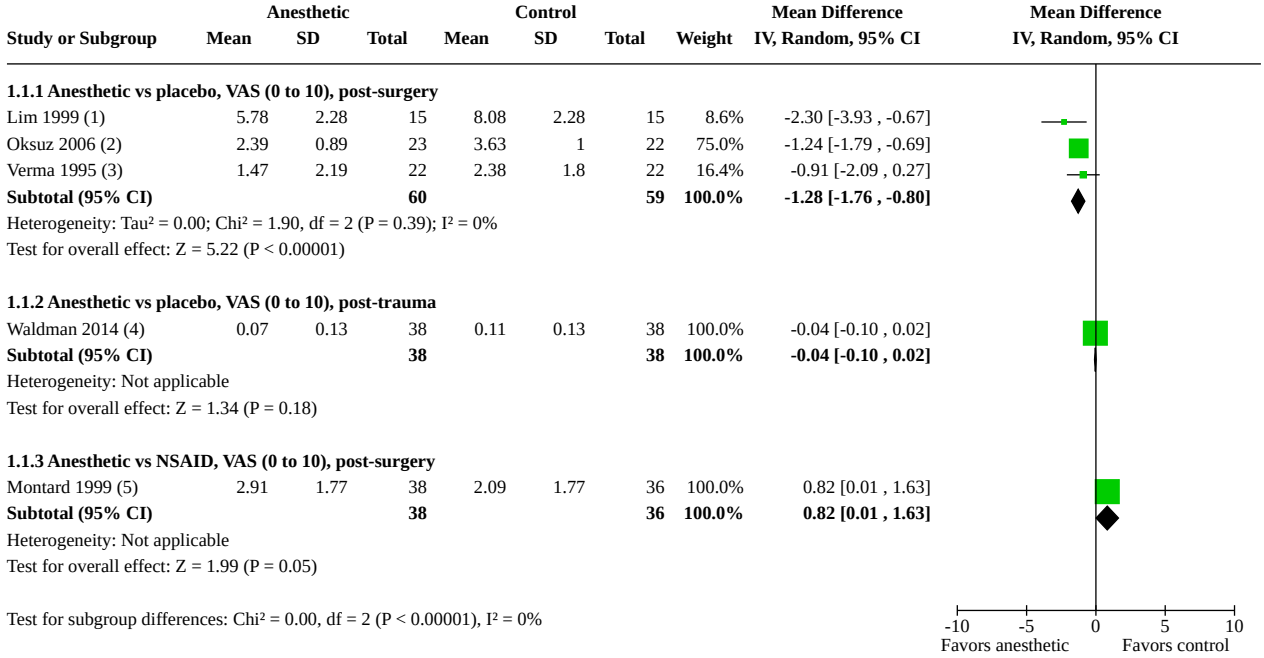
Critical outcomes

Pain control from baseline to 24 hours after treatment initiation

Three post-surgical trials (Lim 1999; Oksuz 2006; Verma 1995) and one post-trauma trial (Waldman 2014) comparing topical anesthetics with placebo reported pain control at this time point. One additional post-surgical trial compared topical tetracaine with diclofenac (Montard 1999).

The combined estimate for pain scores reported by post-surgical participants at 24 hours suggested that when compared with placebo, topical anesthetics reduced pain by 1.28 points on a 10-point scale (MD −1.28, 95% CI −1.76 to −0.80; 3 RCTs, 119 participants; Figure 4) (Lim 1999; Oksuz 2006; Verma 1995). The authors of Waldman 2014 reported pain scores as model-predicted values based on averaging multiple measurements over the first post-intervention 24 hours. Based on the raw data provided by the author team, the single-study estimate, converted from a 100-point to a 10-point scale, was derived from 76 participants (61% of 124 randomized) and showed no evidence of a difference in pain control by 24 hours (MD −0.04 points, 95% CI −0.10 to 0.02).

Figure 4. Forest plot of comparison 1: topical anesthetic vs placebo, outcome: 1.1 Change in participant-reported ocular pain from baseline to 24 hours



Footnotes

(1) At day 1, proparacaine 0.05%, SD from reported P values
(2) At 10 hours, lidocaine 2%
(3) At 24 hours, tetracaine 1%
(4) At 24 hours, tetracaine 1%, converted VAS scores (original scale 0 to 100), individual level data provided by the author team
(5) Average over 24 hours, tetracaine 1% versus diclofenac 0.1%, imputed SD from reported P value of 0.05

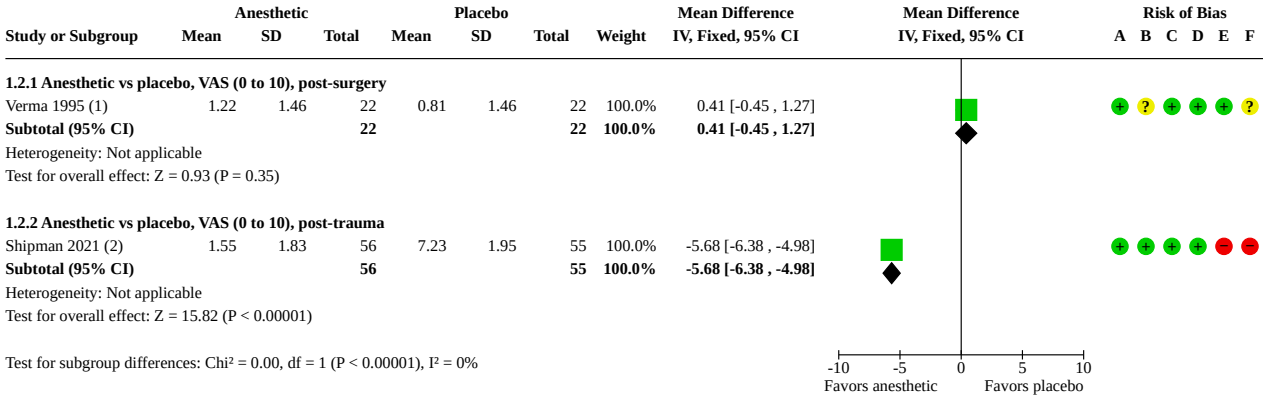
The investigators of Montard 1999 recruited 74 participants who had undergone PRK and reported this outcome by comparing topical tetracaine 1% (every 30 minutes for 24 hours) with diclofenac 0.1% (four times a day for three days). The single-study estimate indicated an 0.82-point higher pain score (on a 10-point VAS) in the tetracaine group than in the diclofenac group (MD 0.82, 95% CI 0.01 to 1.63). We did not combine data across subgroups because of heterogeneity between them (I^2 = 93%). The overall level of certainty of the effect estimates based on the available evidence is very low because of high risk of bias (−2 levels) associated with incomplete data and imprecision (−1 level) from small sample sizes.

Pain control from baseline to 48 hours after treatment initiation

One post-surgical trial (Verma 1995) and two post-trauma trials (Shipman 2021; Waldman 2014) compared pain control by 48 hours for tetracaine versus placebo. We did not include Waldman 2014 in this analysis given the substantial proportion of participants lost to follow-up (and thus the risk of attrition bias); the data for only 43% of 124 randomized participants (tetracaine n = 26; saline n = 27) were reported, according to the information provided by the authors.

The single post-surgical trial reported 0.41-point greater pain in the anesthetic group on a 10-point scale, showing little to no effect on pain control compared with placebo (MD 0.41, 95% CI −0.45 to 1.27; 44 participants; Figure 5) (Verma 1995). The post-trauma trial had an estimated mean difference of 5.68 points (on a 10-point scale), indicating that there may be a large reduction in pain when comparing topical anesthesia versus placebo (MD -5.68, 95% CI -6.38 to -4.98; 111 participants; Figure 5) (Shipman 2021), which is different in direction and magnitude from the estimate from Verma 1995. We did not pool these two trials for analysis because of substantial statistical heterogeneity (I^2 = 99%). The overall certainty of evidence was very low because of high risk of bias (−2 levels), due to missing data and selective outcome reporting, imprecision (−1 level), and inconsistency (−1 level).

Figure 5. Forest plot of comparison 1: topical anesthetic vs placebo, outcome: 1.2 Change in participant-reported ocular pain from baseline to 48 hours



Footnotes

(1) At 48 hours, tetracaine 1%
(2) At 24 to 48 hours, tetracaine 0.5%

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Pain control from baseline to 72 hours after treatment initiation

Based on data from one post-surgical trial, topical anesthetics had little to no effect on self-reported pain measured on a 10-point VAS at 64 hours (MD 0.49 point, 95% CI −0.06 to 1.04; 44 participants; Analysis 1.3) (Verma 1995). The overall certainty of evidence was very low because of risk of bias (−1 level), indirectness (−1 level), and imprecision (−1 level) from the small sample size.

Pain control reported at other time points

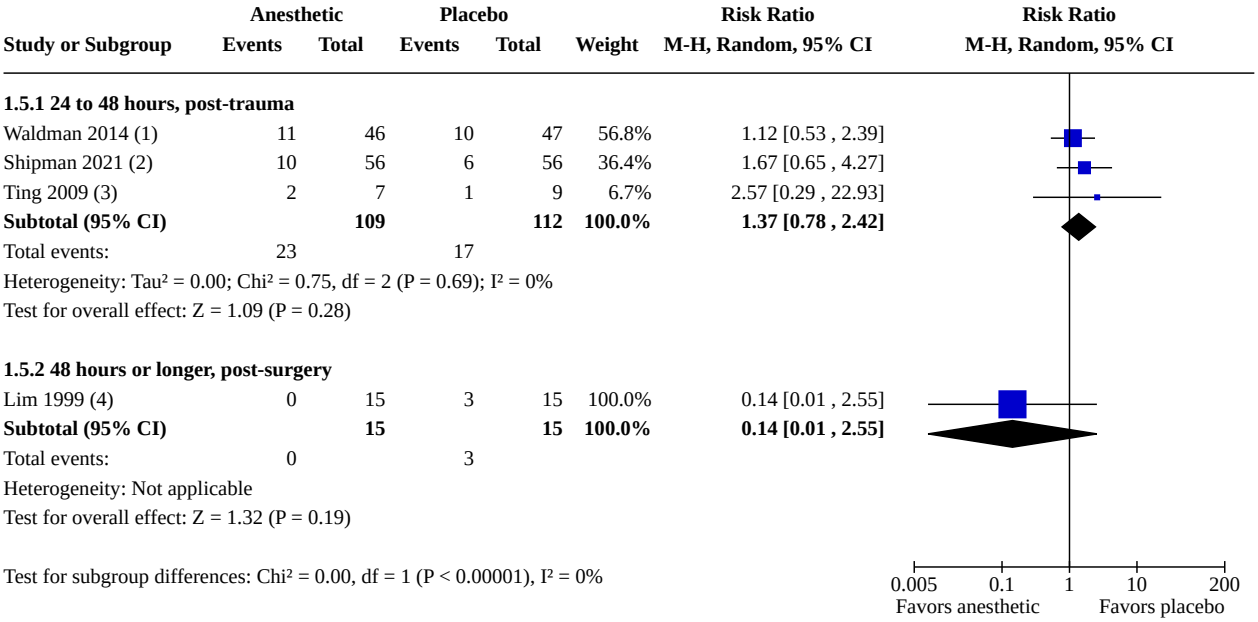
One trial reported the mean cumulative pain score of 12 assessments over 36 hours for 55% (12/22) of tetracaine participants and 36% (9/25) of saline participants initially randomized (Ting 2009). The topical anesthetic group had a lower mean cumulative pain score of 404 (SD 75) compared with 629 (SD 172) for saline on a 100-point scale.

Another two trials reported a seven-day mean or median change in pain scores immediately before and after the use of study drops (Ball 2010; Shahinian 1997). Ball 2010 reported the seven-day median change in pain score five minutes after using the study drops. The proparacaine group had a median improvement of 3.9 points on a 10-point scale (IQR 1.5 to 5.1; n = 15) compared with a median of 0.6 points (IQR 0.2 to 2.0; n = 18) in the placebo group (P = 0.007, reported in Ball 2010). Shahinian 1997 reported the seven-day mean change in pain score one minute after using study drops for 45 of 48 eyes. The proparacaine group had a larger decrease in mean pain (mean −1.75 points, SD 0.69) compared with placebo (mean −0.85 points, SD 0.98) on a 10-point VAS (P < 0.002, reported in Shahinian 1997).

Epithelial healing by 24 to 72 hours

Five trials reported proportions of eyes without complete resolution of epithelial defects by 24 to 72 hours for anesthetics compared with placebo (Lim 1999; Shipman 2021; Ting 2009; Verma 1995; Waldman 2014). Three post-trauma trials formed a subgroup with different concentrations of tetracaine; results of meta-analysis for this subgroup provided no evidence of a difference in epithelial healing when tetracaine was compared with placebo (RR 1.37, 95% CI 0.78 to 2.42; 221 participants; I^2 = 0%; Figure 6) (Shipman 2021; Ting 2009; Waldman 2014). There were insufficient data to explore any dose-response relationship.

Figure 6. Forest plot of comparison 1: topical anesthetic vs placebo, outcome: 1.5 Proportion of eyes without complete resolution of epithelial defects by 24 to 72 hours



Footnotes

(1) At 48 hours, tetracaine 1%
(2) At 24 to 48 hours, tetracaine 0.5%
(3) At 36 to 48 hours, tetracaine 0.4%
(4) At 72 hours, proparacaine 0.05%

In one post-surgical trial, all participants' corneal abrasions had healed by 24 to 72 hours (Verma 1995); there was no evidence of a difference in effect between treatment groups in the other post-surgical trial (Lim 1999) (RR 0.14, 95% CI 0.01 to 2.55; 30 participants; Figure 6).

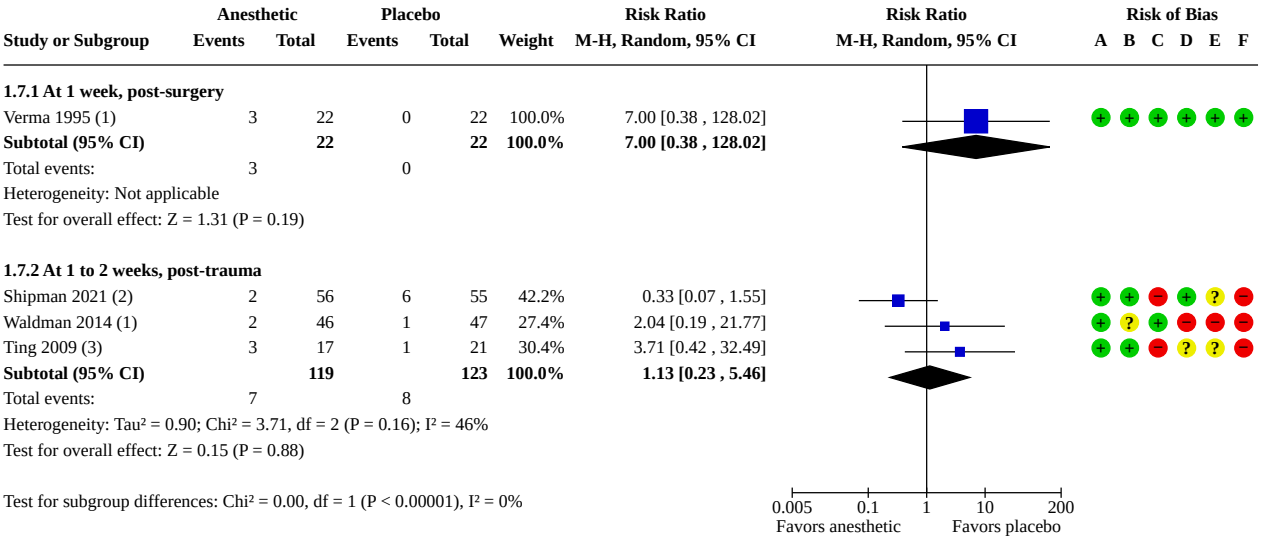
We calculated the risk difference (RD) to include the post-surgical trial Verma 1995, in which epithelial healing had occurred in all eyes in both treatment groups. Analysis by the duration of anesthetic use showed no evidence of differences in the resolution of epithelial defects across trial settings (post-surgical or post-trauma) or treatment duration (Analysis 1.6). However, the evidence is of very low certainty because of risk of bias (−1 level), inconsistency (−1 level), and imprecision (−1 level).

Complications reported by the longest follow-up time

Seven trials reported the number or proportion of participants with complications by the longest follow-up time for topical anesthetics compared with placebo (Ball 2010; Lim 1999; Oksuz 2006; Shipman 2021; Ting 2009; Verma 1995; Waldman 2014).

In the post-surgical trials, no complications were reported in either treatment group for two trials: Lim 1999 up to one week and Oksuz 2006 up to 48 hours. In Verma 1995, the longest follow-up was six months, although adverse events were reported at the week one postoperative clinical assessment. In Verma 1995, at one week, three participants in the tetracaine group experienced gritty sensation in the eye (n = 1), blurred vision (n = 1), and heaping of the epithelium (n = 1) compared with zero complications in the placebo group. The 95% CI of the estimated RR, despite crossing the line of no effect, is very asymmetric in favor of placebo (RR 7.00, 95% CI 0.38 to 128.02; 44 participants; Figure 7). The authors also stated that 20% of the trial participants experienced nausea and vomiting attributed to the oral analgesia (paracetamol/dextropropoxyphene), but no episodes were reported by the treatment group (Verma 1995).

Figure 7. Forest plot of comparison 1: topical anesthetic vs placebo, outcome: 1.7 Proportion of individuals/eyes with complications at furthest time point



Footnotes

(1) At 1 week, tetracaine 1%
(2) At 1 week, tetracaine 0.5%
(3) At 2 weeks, tetracaine 0.4%

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Among the post-trauma trials, Ball 2010 reported no adverse events in either treatment arm. Ting 2009 reported complications at the two-week phone interview. Meta-analysis of complications reported from the other three post-trauma trials provided an estimated RR of 1.13 (95% CI 0.23 to 5.46; 242, 3 RCTs; Figure 7) (Shipman 2021; Ting 2009; Waldman 2014). In the anesthetic group, the adverse events included infiltrate (n = 1), opaque scar (n = 1), worsening of the corneal abrasion (n = 2), and visual problems (n = 1). In the placebo group, the adverse events included recurrent corneal erosion (n = 1), worsening corneal abrasion (n = 2), residual foreign body (n = 2), uncontrolled pain (n = 2), and persistent redness and blurred vision or visual problems (n = 4).

We performed a separate analysis, including trials without events in either arm (see Differences between protocol and review). In Oksuz 2006, the authors stated, "we did not observe any corneal epithelial or ocular surface complications in either group" up to 48 hours. At one week, Ball 2010 reported "no ocular complications" and Lim 1999 stated "no keratitis was observed." The combined risk difference (RD) of 0.01 (95% CI −0.03 to 0.05; 7 RCTs, 394 participants; Analysis 1.8) indicated no evidence of a difference between topical anesthetic and placebo. Overall, the certainty of evidence was very low because of risk of bias (−1 level) and extreme imprecision (−2 levels).

Important outcomes

Treatment failure by 72 hours after treatment initiation

One study had no treatment failures by 72 hours; no oral analgesia was used for eye pain in either treatment group from 24 hours to two weeks (0/17 in the tetracaine compared with 0/21 in the saline group; Ting 2009). The evidence was very low certainty because of risk of bias (−1 level) and imprecision (−2 levels) from the small sample size.

Quality of life

None of the included trials assessed this outcome.

Comparison 2: Anesthetics plus NSAID versus placebo

Critical outcomes

Pain control from baseline to 24 hours after treatment initiation

Only one post-surgical trial compared an anesthetic plus an NSAID with placebo (Lim 1999). The single-study effect estimate showed a large effect of the anesthetic plus NSAID on reducing pain scores at 24 hours when compared with placebo (MD -5.72 on a 10-point scale, 95% CI -7.35 to -4.09; 30 participants; Analysis 2.1). The certainty of evidence was very low because of risk of bias (−1 level) and imprecision from the small sample size (−2 levels).

Pain control from baseline to 48 hours after treatment initiation

None of the included trials reported this outcome.

Pain control from baseline to 72 hours after treatment initiation

None of the included trials reported this outcome.

Epithelial healing by 24 to 72 hours

From data reported in Lim 1999, we found no evidence of an effect on epithelial healing when we compared proparacaine 0.05% plus diclofenac 0.1% with placebo (RR 0.33, 95% CI 0.04 to 2.85; 30 participants; Analysis 2.2). The certainty of evidence was very low because of risk of bias (−1 level) and imprecision (−2 levels).

Complications reported by the longest follow-up time

In Lim 1999, the authors stated that there were no incidences of keratitis during the one-week treatment period. Data from Lim 1999 also indicated no evidence of a difference in ocular adverse effects between topical proparacaine 0.05% plus diclofenac 0.1% versus placebo (RD 0.00, 95% CI −0.12 to 0.12; 30 participants; Analysis 2.3). The certainty of evidence was very low because of risk of bias (−1 level) and imprecision (−2 levels).

Important outcomes

Treatment failure by 72 hours

None of the included trials reported this outcome.

Quality of life at the longest follow-up time

None of the included trials reported this outcome.

DISCUSSION

Summary of main results

In this review, we included nine randomized controlled trials (RCTs) that enrolled 314 post-trauma participants (4 RCTs) and 242 post-surgical participants (five RCTs) to evaluate the effectiveness and safety of topical anesthetics for relief of pain from corneal abrasion. For all outcomes of interest, the evidence that there was any important statistical or clinical difference in benefit or harm between topical anesthetic and placebo was of very low certainty because of risk of bias, outcomes that were not reported, and small sample sizes in the included trials.

The certainty of evidence that topical anesthetics have little or no effect on reducing participant-reported ocular pain at 24 hours for corneal abrasion after surgery or after accidental trauma when compared with placebo or a nonsteroidal anti-inflammatory drug (NSAID) was very low. Topical anesthetics combined with an NSAID may decrease pain at 24 hours relative to placebo in post-surgical participants (one RCT; very low certainty). Very low-certainty evidence suggested that topical anesthetics have little or no benefit over placebo in alleviating ocular pain by 48 or 72 hours in post-surgical participants. Compared with placebo, topical anesthetics may improve pain at 48 hours in post-trauma participants, based on evidence of very low certainty from one trial. Topical anesthetics alone or with an NSAID may not affect the resolution of epithelial defects by 24 to 72 hours after initiation of treatment (five RCTs; very low certainty). Of the seven trials that reported assessing adverse events, the longest follow-up ranged from six months (post-PRK) to 48 hours (post-pterygium surgery) with complications reported at one to two weeks. Although the evidence was of very low certainty, we found no statistical difference in adverse events at longest follow-up between anesthetic and placebo. There were insufficient data comparing the adverse effects of topical anesthetics plus NSAID with a placebo (one RCT).

Overall completeness and applicability of evidence

Overall, there was a paucity of evidence for the comparison of efficacy or safety of topical anesthetics compared with placebo for corneal epithelial defects of traumatic or post-surgical origin. We included randomized trials that were characterized by clinically relevant participants, routinely prescribed interventions, and patient-important outcomes, and found the applicability of the review findings to be limited. The evidence was of very low certainty for all outcomes primarily because of small sample sizes and high risk of bias in two of the five bias domains addressed (missing outcome data and selection of study outcomes for which results had been reported).

Population representativeness

We included trials that enrolled participants with corneal abrasions of various etiologies to optimize the applicability of the review findings. However, there were systematic differences in the direction and magnitude of effect estimates between trials of post-trauma versus post-surgical participants. Because there were too few trials for meaningful statistical subgroup analysis, we do not know the degree to which etiology may influence specific effects. For these reasons, we did not combine outcome data from post-trauma participants with those from post-surgical participants.

The findings are not applicable to pediatric populations as there was no participant younger than 17 years of age. We were interested in exploring treatment effects by gender and race, but none of the included trials provided sufficient information. There is an increasing awareness of the role that race and ethnicity may play in pain management (Booker 2023; Campbell 2012; Letzen 2022). Unfortunately, only one study reported the ethnicity of participants but did not report outcomes by ethnicity (Waldman 2014). The authors also discussed the influence of community culture on self-reported pain but did provide further details (Waldman 2014).

For the comparison of anesthetic versus placebo, eight of the nine trials reported the gender of participants. The predominance of male participants across the four included trials in emergency departments was consistent with previously published US surveys (Channa 2016; McGwin 2005). In the only trial that tested the combination of anesthetic and NSAID against placebo, the authors did not report the gender ratio of participants within each treatment arm (Lim 1999). On average, there was a higher proportion of women enrolled in trials of post-ophthalmic surgeries than in those conducted in the emergency department setting (60% versus 21%, respectively). Given the growing body of literature suggesting gender differences in pain perception and reporting (Racine 2012a; Racine 2012b), the difference in gender ratios across trials and between the two main etiologies of corneal abrasions in this review may have contributed to the heterogeneity of the observed treatment effect.

Interventions

The nine included trials evaluated three of the commonly used topical anesthetics: proparacaine (Ball 2010; Lim 1999; Shahinian 1997), tetracaine (Montard 1999; Shipman 2021; Ting 2009; Verma 1995; Waldman 2014), and lidocaine (Oksuz 2006). There was only one trial in which participants received an amide anesthetic

(lidocaine) in three doses over three hours prior to discharge (Oksuz 2006). The other eight trials discharged participants with ester anesthetics: tetracaine at different concentrations with a duration of 24 to 48 hours and dilute proparacaine 0.05% for one week in three trials. The total amount dispensed and the frequency of use varied, but it was not always reported. Because of the very low certainty of evidence regarding critical outcomes, we cannot address concerns about anesthetic abuse from short-term use of tetracaine by participants.

Co-interventions in several trials may confound the effects of anesthetic use and contribute to the observed heterogeneity. Depending on the trial, oral analgesia was prescribed as needed for breakthrough pain, used on a schedule to prevent breakthrough pain, or simply not permitted. Antibiotic use differed across trials by type and duration. There were also differences in the use of bandage contact lenses, occlusive patches, and supplemental topical anesthetics.

The review findings are most applicable to ester anesthetics compared with placebo. We did not find trials comparing topical anesthetics with other common treatments, such as topical cycloplegics, and only one trial compared anesthetics with NSAIDs (Montard 1999). We found only one trial with dual therapy: NSAID plus anesthetic (Lim 1999).

Outcome measurement

None of the included trials assessed health-related or vision-related quality of life or functions of daily activity. Thus, although pain is multidimensional in nature, we cannot extrapolate the very low-certainty evidence of topical anesthetic efficacy beyond the effects on pain intensity. There is concern that sole reliance on self-reported pain intensity can result in an overestimation of the amount of treatment needed, which is a possible contributor to the overprescribing observed in the opioid epidemic (Pogatzki-Zahn 2019; Sharfstein 2019).

All the pain intensity measurements could be converted to 10-point scales, which are ubiquitous and commonly used in both clinical practice and randomized trials. Similar clinically important change in pain intensity was defined in three trials, ranging from 1.5 to 2 points on a 10-point scale (Ball 2010; Shipman 2021; Waldman 2014). These definitions overlap with other reviews of interventions for acute pain, which have defined 'moderate' effects as a change of 1 to 2 points, and 'substantial' effects as greater than a change of 2 points on a 10-point scale (Chou 2020). One trial noted that lower than 3 on a 10-point scale is an accepted target for patients with a baseline of moderate to severe pain (Verma 1997). However, the trials included in this review were small, and only half reported participants' baseline pain, which makes it difficult to assess the sensitivity to detecting analgesic effects (Brinck 2018; McQuay 2012; Moore 2013).

Although the pain intensity scales used in the included trials are comparable, the timing of pain intensity measurements (e.g. at 24, 48 hours; change from before and one, three, or five minutes after use of study drops), method of aggregation (e.g. score at 10 hours; overall mean scores up to 24, 48 hours; total pain burden), and type of analysis (e.g. reported value, mixed-model for multiple time points, single factor analysis) were different in each trial. Other Cochrane Reviews of treatments for corneal abrasions found similar issues with outcome specification and reporting (Algarni 2022; Lim 2016; Wakai 2017).

We sought to assess the proportion of participants who did not have sufficient pain control from topical anesthetics during the periods assumed to be most painful. All the included trials had the highest pain recorded between baseline and 72 hours, but only one trial reported treatment failure over that time period (Ting 2009).

The proportion of participants who did not return for follow-up at emergency departments was much higher than the proportion of participants not followed up in the trials conducted in the setting of ophthalmic surgery. In some of the trials conducted in the emergency department, ophthalmologists assessed participants, but most assessments were performed by emergency physicians. These provider differences in outcome measurement and assessment (interpretation) may have contributed to the clinical heterogeneity associated with the different trial settings and etiology of abrasions. The authors of Ting 2009 state that only 34% (16/47) of the randomized participants returned for follow-up at 36 to 48 hours and, therefore, the evidence remains "inconclusive" whether topical anesthetics prescribed for poor pain control after trauma could delay corneal epithelial healing. Most participants cited insignificant pain or no pain and absence of visual problems as the main reasons for noncompliance with return for follow-up.

The majority of trials did not report adverse events beyond one week, and only three trials reported specific adverse events. In this review we sought to synthesize the evidence in light of ongoing concerns raised by case reports and case series regarding the risks of delayed healing and ocular morbidity due to topical anesthetic abuse. The majority of cases report adverse events at time points well beyond those of the trials in this review (Aksoy 2013; Ansari 2006; Ardjomand 2002; Chen 2004; Chern 1996; Dornic 1998; Epstein 1968; Katsimpris 2007; Khakshoor 2012; Kim 1997; Lee 2008; Pharmakakis 2002; Rosenwasser 1990; Varga 1997; Webber 1999; Willis 1970; Wu 2016; Yagci 2011). For example, in Turkey, where topical anesthetics were available over the counter until 2012, one study found that median drug use was 28 days (range: 10 to 112 days; seven patients) before admission to clinic for amniotic membrane transplantation (Burcu 2013). Another case series reported that epithelial healing took a median of 17 days (range: 6 to 50 days; 19 patients) in patients diagnosed with topical anesthetic abuse keratopathy (Yagci 2011). The findings of the current review cannot address whether these cases of anesthetic abuse are outliers or the norm since the majority of included trials did not clinically assess safety outcomes beyond one to two weeks.

The time from the corneal abrasion to participant randomization was longer in the acute trauma setting than the post-surgical setting by 24 to 36 hours, depending on the trial. Post-trauma trials varied in whether investigators included patients with rust rings, which has implications for potential risk of bias and for the applicability of findings. In the post-surgical trials, the abrasion depth and area were more uniformly controlled and created in a sterile field. The baseline risk for healing time and adverse events such as microbial keratitis may differ systematically by setting.

Certainty of the evidence

We downgraded the certainty of evidence for most review outcomes because of risk of bias from missing outcome data and selection of the outcome results that had been reported,

and because of imprecision of effect estimates based on small sample sizes. Aside from the clinical heterogeneity in the trial design and conduct (trial setting, dosage of intervention and co-intervention, outcome measurement, method of aggregation, types of analysis, time of outcome assessment, and duration of follow-up) and in patient characteristics (etiologies of abrasion, presence or absence of rust rings, which might have influenced dropout from post-trauma trials), other reasons for the observed statistical heterogeneity included differences in the directions of effects between trials. The small number of trials limited our ability to explore these factors in depth. Of the nine included trials, we found trial registration records for only four trials; only one had been registered before participant enrollment began.

Potential biases in the review process

We aimed to minimize potential biases in the review process by applying standard Cochrane methodology. We contacted study authors during the screening of full-text reports to minimize the exclusion of eligible trials. We clarified with investigators regarding conflicting information found in reports from the same study, trials halted prior to enrollment, and clarifications of issues regarding randomization. We did not exclude the one study for which we did not receive a response (Aseff 1997). We also received raw data for two outcome time points from one of the authors (Waldman 2014). We included trials regardless of language of publication and translated study reports to the extent necessary (Lim 1999; Montard 1999). One limitation of this review is that estimates of rates of serious adverse events may be under-reported either because of rarity, the method of elicitation of reports of complications, or under-reporting by the study investigators. This limitation prevented us from assessing the safety of the intervention to permit readers to balance efficacy and safety.

Agreements and disagreements with other studies or reviews

Three reviews that included multiple interventions for post-PRK pain management have discussed the use of topical anesthetics for pain management (Garcia 2016; Golan 2018; Steigleman 2023). The Golan 2018 review recommended against the long-term use of topical anesthetics, while Garcia 2016 stated that based on three studies (including Verma 1995 in our review), topical anesthetics did not delay epithelial healing. The conclusions of the authors of the third review were more measured and highlighted the need for careful monitoring (Steigleman 2023). Different inclusion criteria may account for these varying conclusions as both Golan 2018 and Steigleman 2023 included the same trials, while the Shahinian 1997 trial was omitted from Garcia 2016. We included two non-English language trials that were excluded from the above reviews based on the publication language (Lim 1999; Montard 1999). Although their inclusion did not provide further certainty regarding the safety or efficacy of topical anesthetics, it highlights the potential for bias introduced by restricting studies included in reviews by language of publication.

A systematic review of RCTs evaluating the safety and efficacy of topical proparacaine and tetracaine for corneal abrasions (Swaminathan 2015) included several studies included in our review (Ball 2010; Waldman 2014; Verma 1995). These authors originally intended to review corneal abrasions seen in the emergency department. However, the selection was expanded to also include patients who underwent PRK because of a paucity of studies identified in their original search. Their conclusion was that topical anesthetics were safe and effective for corneal abrasions either from trauma or after PRK. It is important to note that these authors did not perform a statistical meta-analysis, nor did they quantify the methodological rigor (e.g. risk of bias) of studies or the level of certainty in the data.

A more recent systematic review of RCTs and observational studies included several types of topical interventions for pain control (NSAIDs, bandage contact lenses, patching, topical anesthetics) compared with placebo or no treatment for traumatic corneal abrasions (Yu 2021). They explicitly excluded post-surgical studies. For the comparison of topical anesthetics with placebo, Yu 2021 included the same four randomized controlled trials (RCTs) and one observational study that we excluded (Waldman 2018). Based on this trial, Yu 2021 noted that there may be differences in adverse outcomes based on corneal abrasion complexity (e.g. size of abrasion). Our review did not explore differences in outcomes based on corneal abrasion size. However, it is worth noting that the post-surgical trials did report grouping by the abrasion size. Our review is in agreement with Yu 2021 on the absence of definitive evidence regarding safety outcomes, although our count of participants and complications differs. The reason for this difference may be from the review author's classification of complications and the specified time point. The authors of Yu 2021 recommend, "If topical anesthesia is given to the patient, we advocate for formulations such as dilute proparacaine as opposed to tetracaine, the latter being available in clinics largely to facilitate ocular examination." In our review, there was insufficient evidence, even with the inclusion of post-surgical trials, to support or refute such a recommendation.

We focused solely on topical anesthetics. A number of treatment modalities for pain following PRK were highlighted in Steigleman 2023 but were not included in Yu 2021, possibly reflecting the inherent differences between diagnosis and management of post-surgical epithelial defects and traumatic corneal abrasions.

AUTHORS' CONCLUSIONS

Implications for practice

Corneal abrasions from trauma or epithelial defects created during ophthalmic surgery present commonly in clinical practice. Safely managing pain is therefore of great interest. With a growing opioid crisis in the United States, opioid-sparing pain management is a favorable option. Although topical anesthetics provide excellent pain control in the intraoperative setting, they traditionally have not been prescribed for outpatient use.

Compared with placebo, topical anesthetics alone or combined with a nonsteroidal anti-inflammatory drug (NSAID) have been shown to be effective in reducing pain up to 24 hours in post-surgical patients. Compared with NSAIDs, topical anesthetics may be slightly less effective at pain control in post-surgical patients. At 48 hours, topical anesthetics decreased pain relative to placebo but were no more effective at 72 hours. Very low-certainty evidence regarding complications within seven days favored placebo in post-surgical participants.

Despite a lack of evidence of efficacy or safety differences between topical anesthetic and placebo in accidental or surgically created corneal abrasions, use of anesthetic eye drops without close

monitoring creates a potential for ocular morbidity. We wish to highlight that the studies in this review were characterized by very close follow-up of participants, use of an often diluted anesthetic mixture, and dispensing of a very limited supply. Despite the fact that we found no differences in safety (e.g. complications at longest follow-up) the evidence was of very low certainty and, therefore, we do not discount the case literature describing a typified pattern of abuse. Similar to the use of topical steroids or NSAIDs, the risk of adverse effects increases when anesthetic drops are used more frequently or for longer than recommended. It is not difficult to imagine that a practice pattern shift towards liberalization of topical anesthetic prescribing could lead to situations far beyond the controlled environments of the studies we reviewed: where larger quantities are dispensed, follow-up is not ensured, or where other providers reflexively renew prescription refills. Furthermore, case series in the ophthalmic literature indicate that patients who abuse topical anesthetics may have a psychiatric disorder, history of drug abuse, or history of depression. It is possible that such patients demand anesthetic agents because of heightened pain awareness. However, it is not clear whether emergency rooms have the resources to screen patients for these disorders prior to prescribing topical anesthetics and to counsel them on the importance of follow-up with an ophthalmologist. All trials included in this review were characterized by very short follow-up, which may not have allowed such complications to manifest. Patients recruited in the emergency department setting had higher dropout rates than post-surgery patients, which raises the potential for misuse compared with surgical patients who have close follow-up by an ophthalmic surgeon for a defect created in a sterile field. The latter may be reasons for newer modalities to be used to treat post-photorefractive keratectomy pain that may be inappropriate for use to relieve pain from abrasions that present in non-surgical settings.

Implications for research

- Investigators planning future trials on the safety and efficacy of topical anesthetics should plan for a larger sample size of diverse participant populations and both shorter (e.g. first eight hours) and longer (e.g. over one week) follow-up periods to assess critical outcomes and rare or non-immediate complications. Sample size assumptions (effect size, power) should be justified. Traumatic corneal abrasions account for more than 10% of eye-related emergency room visits, which would indicate the potential for RCTs with larger enrollment than the RCTs in this review. Attrition should be reported and investigated, with attempts made to contact such patients for possible risk of anesthetic abuse. One concern with topical anesthetics prescribed on an outpatient basis for corneal abrasions is that patients who obtain prescriptions from multiple emergency rooms and do not follow up with either an emergency room physician or an ophthalmologist are at risk for anesthetic abuse-related corneal complications. The situation would be analogous to the opioid crisis where providers were not versed in prescribing opioids (or in some cases were incentivized) and patients became addicted.
- Efficacy outcomes should include a more complete understanding of pain; participant-reported functional and quality of life assessment should be used alongside pain levels at baseline and follow-up. There are core outcome sets being developed that should be considered in future trials and reviews.
- Investigators of future trials should collect data on adjunct opioid pain control, as there is a nationwide push for reduced opioid pain management due to the ongoing opioid addiction crisis.
- Investigators of future trials should also avoid or reduce the potential sources of bias identified in this review, such as selection bias caused by differential attrition rates at follow-up and information bias introduced by complete-case analysis when the proportion of missing outcome data is substantial.
- Investigators should report outcomes by treatment arm both overall and within sex/gender and race/ethnicity subgroups of participants.
- Investigators should differentiate between abrasions with complications (e.g. rust rings) and abrasions without complications to increase the applicability of the evidence to difference patient groups.

ACKNOWLEDGEMENTS

Acknowledgments from the authors

We thank Barbara Hawkins for her comments and methodology guidance on the protocol and review. We acknowledge the Cochrane Pain, Palliative and Supportive Care (PaPaS) resources on acute pain and thank Neil O'Connell, PaPaS Co-ordinating Editor, and Andrew Moore, former PaPaS Senior Editor, for their comments on pain outcomes at the protocol development stage.

Editorial and peer reviewer contributions

CEV@US supported the authors in the development of this review. The following people conducted the editorial process for this review:

- Sign-off Editors (final editorial decision): Dr. Tianjing Li (University of Colorado Anschutz Medical Campus), Gianni Virgilli (Queen's University Belfast, Ireland; University of Florence, Italy), Barbara Hawkins (Johns Hopkins University)
- Managing Editor and Assistant Managing Editor (selected peer reviewers, collated peer reviewer comments): Anupa Shah (Queen's University Belfast); Genie Han (Johns Hopkins University)
- Information Specialist: Lori Rosman (Johns Hopkins University)
- Copy Editor: Jenny Bellorini (Cochrane Central Production Service)
- Peer reviewers: Miles Greenwald (Kellogg Eye Center), Chris Lim (Royal Melbourne Hospital)

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ball 2010

Study characteristics	
Methods	**Study design:** parallel RCT **Unit of randomization:** individual (1 eye included) **Study start date:** 10 January 2005

Ball 2010 *(Continued)*

	Study end date: 9 January 2006 **Participant follow-up time:** 1 week **Treatment time:** 1 week **Time from abrasion to randomization (hours):** 24 **Power calculation:** "We determined that 16 participants in each group would be needed to have an 80% chance of detecting a pain reduction of 2 cm on the visual analog scale between the 2 groups, assuming an α of 0.05, and a standard deviation of 2 cm. We chose 2 cm to represent a clinically meaningful difference based on an informal survey of attending emergency physicians at our hospital."
Participants	**Country/countries:** Canada **Setting:** 2 tertiary care emergency departments **Inclusion criteria:** adult patients with acute (within 24 hours) traumatic corneal injuries **Exclusion criteria:** immunocompromised, known allergy to local anesthetic, unable to consent/follow instructions for dosing/go to follow-up appointments, previous ocular pathology **Reported a subgroup analyses (Y/N):** no **Total randomized (n):** 43, not reported by group **Exclusions and loss to follow-up (n; reasons):** 11, not reported by group; noncompliance with treatment **Analyzed (n):** 33 Proparacaine 0.05% group: 15 Placebo group: 18 **Age (mean ± SD, range):** no total Proparacaine 0.05% group: 38.0 (28.0 ± 47.0) Placebo group: 39.3 (27.0 ± 46.0) **Gender (number, % female):** 5 (15%) Proparacaine 0.05% group: 2 (13%) Placebo group: 3 (17%) **Race/ethnicity (study definition, n, %):** not reported **Etiology of corneal abrasion (study definition, n, %):** not reported **Baseline pain (study scale):** not reported
Interventions	**Interventions** proparacaine 0.05% (diluted from proparacaine 0.5%), 2 to 4 drops as needed for 7 days, 40 mL total dispensed **Comparison:** "colour- and smell-matched placebo", 2 to 4 drops as needed for 7 days, 40 mL total dispensed **Co-interventions:** 1. Topical gatifloxacin, 1 drop every 2 hours for 7 days 2. Oral acetaminophen 325 mg with 30 mg of codeine, 1 to 2 tablets every 4 hours if needed, for 7 days
Outcomes	**Primary study outcome(s):** 1. Pain reduction from baseline as measured on a 10 cm VAS (0 to 10; 0 = "no pain", 10 = "the worst imaginable pain"). Mean difference in pain scores before and 5 minutes after drug administration as recorded by each study participant **Secondary study outcome(s):** 1. Patient satisfaction with the study drug at 5 days post injury on a 10 cm VAS (0 to 10; 0 = "completely unsatisfied", 10 = "completely satisfied") 2. Median number of drops of the study drug that patients self-administered each time the study drug was used 3. Median time interval between administration of the first and last drop of study drug for each time the study drug was used 4. Median number of tablets of acetaminophen (300 mg) with codeine (30 mg) used after administration of the study drug 5. Signs of delayed wound healing at days 3, 5, and 7 post-injury 6. Corneal toxicity on follow-up

Ball 2010 *(Continued)*

	Adverse event(s): ophthalmologist to assess for increased corneal thickness, corneal opacification, new corneal epithelial defects, or any other ocular pathology that could be related to either the initial injury or the use of study medication **Measurement time points:** all patients attended for follow-up at an outpatient clinic on days 1, 3, 5, and 7
Notes	**Sponsorship source:** not reported **Conflicts of interest:** "none" declared **Informed consent obtained?:** yes **Ethics approval obtained?:** yes **Investigator's name:** Ian Michael Ball **Affiliated institution:** Divisions of Emergency Medicine and Critical Care Medicine, Department of Medicine, London Health Sciences Centre **Trial registration ID:** NCT00620997

Lim 1999

Study characteristics	
Methods	**Study design:** parallel RCT **Unit of randomization:** individual (1 eye included) **Study start date:** November 1997 **Study end date:** April 1998 **Participant follow-up time:** 1 week **Treatment time:** 1 week **Time from abrasion to randomization (hours):** 0 **Power calculation:** not reported
Participants	**Country/countries:** South Korea **Setting:** ophthalmology surgery **Inclusion criteria:** excimer laser PRK **Exclusion criteria:** pregnant, acute systemic inflammation, hypersensitivity to eye drops, pre-existing corneal disease, glaucoma, retinal disease, or a history of other ophthalmic surgeries; use of analgesic, systemic, or eye drop steroids within 48 hours before surgery **Reported a subgroup analysis (Y/N):** no **Total randomized (n):** 45* **Exclusions and loss to follow-up (n; reasons):** not reported **Age (mean ± SD, range):** 27.8 (range 20 to 42), not reported by group **Race/ethnicity (study definition, n, %):** not reported **Etiology of corneal abrasion (study definition, n, %):** PRK (45, 100%) **Gender (number, % female):** 75, 71%; not reported by group **Race/ethnicity (study definition, n, %):** not reported **Etiology of corneal abrasion (study definition, n, %):** PRK (45, 100%) **Baseline pain (study scale):** Proparacaine 0.05% group: not reported Proparacaine 0.05% + diclofenac 0.1% group: not reported Artificial tears group: not reported *Data from 60 participants randomized to ineligible comparisons were excluded from this review (15 participants in 4 groups)
Interventions	**Intervention 1:** proparacaine 0.05% (diluted from Alcaine 0.5%, Alcon), 1 drop every 4 hours for 1 week **Intervention 2:** diclofenac I 0.1% (Naclof, Cibar-Geigy) plus proparacaine 0.05% (diluted from Alcaine 0.5%, Alcon), 1 drop every 4 hours for 1 week **Comparison:** artificial tears (Tears Naturale, Alcon), 1 drop every 4 hours for 1 week **Co-interventions:**

Lim 1999 *(Continued)*

	1. Topical homatropine 1%, instilled once after surgery 2. Therapeutic contact lenses until the corneal epithelial defect is completely healed 3. Topical ofloxacine, every 6 hours for 1 week 4. Mefenamic acid oral tablets for breakthrough pain **Ineligible interventions excluded from this review:** 1. Suprofen 1% (Profenal, Alcon), 1 drop every 4 hours for 1 week 2. Diclofenac I 0.1% (Naclof, Cibar-Geigy), 1 drop every 4 hours for 1 week 3. Diclofenac II 0.1%(Decrol, 일양약품), 1 drop every 4 hours for 1 week 4. FluorometholOne (fluorometholone, Santen), 1 drop every 4 hours for 1 week
Outcomes	**Primary study outcome(s):** 1. Pain intensity VAS (0 to 10; 0 was no pain at all, and 10 was the most severe pain experienced) 2. Glare at every visit (light sensitivity) and the subjective degree of tearing, 0: none, 1: slightly present, 2: severe, and 3: very severe, respectively 3. Residual epithelial defect area, slit lamp exam 4. Sleeping hours the first night following surgery 5. Degree of burning sensation during eye drop application (0 to 3; 0: not stinging, 1: slightly stinging, 2: very stinging, and 3: too severe to be administered) 6. Number of days until it was possible to return to daily life **Secondary study outcome(s):** not reported **Adverse event(s):** keratitis or corneal clouding **Measurement time points:** days 1, 2, 3, 4, and 1 week. All patients were asked to visit every day until the epithelial defect was completely healed after surgery, and they were asked to visit again, 1 week after surgery
Notes	**Sponsorship source:** not reported **Conflicts of interest:** not reported **Informed consent obtained?:** unclear **Ethics approval obtained?:** unclear **Investigator's name:** Hyun Taek Lim **Affiliated institution:** Department of Ophthalmology, College of Medicine, University of Ulsan, Asan Medical Center, Seoul, Korea **Trial registration ID:** not reported

Montard 1999

Study characteristics	
Methods	**Study design:** parallel RCT **Unit of randomization:** individual (1 eye included) **Study start date:** not reported **Study end date:** not reported **Participant follow-up time:** 3 days **Treatment time:** 24 hours **Time from abrasion to randomization (hours)**: 0 **Power calculation:** not reported
Participants	**Country/countries:** France **Setting:** ophthalmology surgery **Inclusion criteria:** patients undergoing PRK **Exclusion criteria:** not reported

Montard 1999 *(Continued)*

	Reported a subgroup analysis (Y/N): Yes; "sex" (male, female), myopia correction (low, medium, strong), previous PRK (first PRK, second eye, retreatment on an eye previously undergone PRK), size of epithelial defect **Randomized (n):** 74 Tetracaine 1% group: 38 Diclofenac 0.1% group: 36 **Exclusions and loss to follow-up (n):** not reported **Exclusion reasons:** not reported **Analyzed (n):** not reported **Age (mean ± SD, range):** mean 30 years old; not reported by group **Gender (number, % female):** 42, 56.8%; not reported by group **Race/ethnicity (study definition, n, %):** not reported **Etiology of corneal abrasion (study definition, n, %):** PRK (74, 100%); 1st surgery (33), 2nd surgery on the other eye (32), 2nd surgery on the same eye/retreatment (9) **Baseline pain:** not reported
Interventions	**Intervention:** tetracaine 1%, every 30 minutes for 24 hours **Comparison:** diclofenac 0.1%, 4 times per day for 3 days **Co-interventions:** • Ofloxacin 0.3% (Exocine), 1 drop 4 times a day for 7 days • Paracetamol-noramidopyrine (Di-antalvic), as needed for pain
Outcomes	**Primary study outcome(s):** 1. Pain: VAS 10 cm (0 to 10 scale; horizontal bar whose two ends correspond to 'absence of pain' and 'maximum imaginable pain') 2. Functional symptoms: this pain is accompanied by a set of local symptoms (tearing, blepharospasm, sensation of intraocular foreign body) and general symptoms (headache, insomnia). For each symptom, there are three numerical scores by assigning the value 0 for absent, the value 5 for minimal and the value 10 for major 3. Epithelial healing: photographs taken in blue light after instillation of fluorescein, a calculation of the corneal surface devoid of epithelium is carried out using the computer. Mean hourly re-epithelialization rate calculated 4. Hours of sleep 5. Analgesic consumption **Secondary study outcome(s):** not reported **Adverse event(s):** not reported **Measurement time points:** pain assessed every hour for 30 hours; epithelial healing assessed on the day of surgery, 1 day and 3 days after surgery
Notes	**Sponsorship source:** not reported **Conflicts of interest:** not reported **Informed consent obtained?:** yes **Ethics approval obtained?:** yes **Investigator's name:** Montard, M **Affiliated institution:** Ophthalmology Department, Minjoz Hospital, Besançon, France **Trial registration ID:** not reported

Oksuz 2006

Study characteristics	
Methods	**Study design:** parallel RCT **Unit of randomization:** individual (1 eye included) **Study start date:** not reported

Oksuz 2006 *(Continued)*

	Study end date: not reported **Participant follow-up time:** 2 days **Treatment time:** 3 hours **Time from abrasion to randomization (hours):** 0 **Power calculation:** not reported
Participants	**Country/countries:** Turkey **Setting:** eye clinic **Inclusion criteria:** patients undergoing pterygium surgery **Exclusion criteria:** glaucoma, previous eye surgery, dementia or mental instability, deafness, hyperanxiety, communication barriers and the inability to complete the VAS **Reported a subgroup analysis (Y/N):** no **Randomized (n):** 45 Lidocaine gel 2% group: 23 Artificial tear gel group: 22 **Exclusions and loss to follow-up (n):** not reported **Exclusion reasons:** not reported **Analyzed (n):** not reported **Age (mean ± SD, range):** overall not reported Lidocaine gel 2% group: 45.52 ± 9.15 Artificial tear gel group: 47.86 ± 9.74 **Gender (number, % female):** 20, 44% Lidocaine gel 2% group: 10, 43% Artificial tear gel group: 10, 45% **Race/ethnicity (study definition, n, %):** not reported **Etiology of corneal abrasion (study definition, n, %):** pterygium surgery (45, 100%) **Baseline pain (study scale):** not reported
Interventions	**Intervention:** lidocaine 2% gel (Xylocaine, AstraZeneca, Mississauga, Canada), 1 mL 1 hour after surgery, and every hour for 3 hours **Comparison:** artificial tear gel (Thilo-Tears Jel, Alcon-Couvreur, Puurs, Belgium), 1 mL 1 hour after surgery, and every hour for 3 hours **Co-interventions:** eyes were patched from the very beginning of the operation to the completion of the corneal re-epithelization
Outcomes	**Primary study outcome(s):** 1. Corneal re-epithelization time was assessed by slit lamp biomicroscopy 2. A 10 cm VAS (0 to 10; 0 = no pain, 10 = unbearable pain) **Secondary study outcome(s):** not reported **Adverse event(s):** side effects related to study drops, corneal epithelial, or ocular complications **Measurement time points:** hours 4, 7, 10, 24. Assessment after hour 24 based on incomplete re-epithelialization, hours 36 and 48
Notes	**Sponsorship source:** not reported **Conflicts of interest:** not reported **Informed consent obtained?:** yes **Ethics approval obtained?:** unclear **Investigator's name:** C. Tamer **Affiliated institution:** Mustafa Kemal University **Trial registration ID:** not reported

Shahinian 1997

Study characteristics	
Methods	**Study design:** parallel RCT

Shahinian 1997 *(Continued)*

	Unit of randomization: individual (48 eyes of 34 persons) **Study start date:** not reported **Study end date:** not reported **Participant follow-up time:** 1 week **Treatment time**: 1 week **Time from abrasion to randomization (hours):** 0 **Power calculation:** not reported
Participants	**Country/countries:** Canada; US **Setting:** ophthalmology surgery (PRK) **Inclusion criteria:** not reported **Exclusion criteria:** not reported **Reported a subgroup analyses (Y/N):** no **Randomized (n):** 48 eyes (34 patients); randomization unit was person Proparacaine 0.05% group: 25 eyes, number of patients not reported Artificial tears group: 23 eyes, number of patients not reported **Exclusions and loss to follow-up (n):** not reported **Exclusion reasons:** not reported **Analyzed (n):** 48 eyes Proparacaine 0.05% group: 25 eyes Artificial tears group: 23 eyes **Age (mean ± SD, range):** not reported **Gender (number, % female):** not reported **Race/ethnicity (study definition, n, %):** not reported **Etiology of corneal abrasion (study definition, n, %):** PRK (48, 100%) **Baseline pain (study scale):** not reported
Interventions	**Intervention:** proparacaine 0.05%, 1 drop 4 times a day for 1 week **Comparison:** artificial tears, 1 drop 4 times a day for 1 week **Co-interventions:** 1. Bandage soft contact lens for the first 48 hours 2. Topical diclofenac 0.1% (Voltaren Ophthalmic, CIBA Vision), 4 times a day for the first 48 hours 3. 0.3% tobramycin and 0.1% dexamethasone (Tobradex, Alcon), 4 times a day for 1 week 4. Oral acetaminophen and hydrocodone bitartrate (Vicodin, Knoll Pharmaceutical), as needed for 1 week
Outcomes	**Primary study outcome(s):** 1. Pain scores before and 1 minute after each study drop use (0 to 10 scale; 0 = "no pain" and 10 = "the worst pain imaginable") 2. Use of oral analgesia **Secondary study outcome(s):** 1. Duration of pain relief (5 categories: "0 to 10 minutes," "10 to 30 minutes," "30 to 60 minutes," "1 to 4 hours," and "more than 4 hours") 2. Pain control helpfulness (3 categories: "not helpful," "somewhat helpful," or "very helpful") 3. Number of days until corneal epithelialization by slit lamp examination **Adverse event(s):** "After surgery, patients were observed daily with slit lamp examination until epithelial healing was reached. The epithelial defect size and any adverse effects were noted" **Measurement time points:** daily for 1 week
Notes	**Sponsorship source:** not reported **Conflicts of interest:** "Dr. Shahinian holds patent rights to either this or a competing drug. All other authors have no proprietary interest in the development or marketing of this or a competing drug." **Informed consent obtained?:** yes **Ethics approval obtained?:** yes

Shahinian 1997 *(Continued)*

Investigator's name: Lee Shahinian Jr
Affiliated institution: Stanford University Department of Ophthalmology
Trial registration ID: not reported
Investigator contact: authors confirmed via email the multiple reports included interim results. We extracted data from the final publication (Shahinian 1997).

Shipman 2021

Study characteristics	
Methods	**Study design:** parallel RCT **Unit of randomization:** individual (one eye included) **Study start date:** 1 May 2015 **Study end date:** 30 September 2018 **Participant follow-up time:** 1 week **Treatment time:** 24 hours **Time from abrasion to randomization (hours):** less than 36 hours **Power calculation:** "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"
Participants	**Country/countries:** US **Setting:** single-center emergency department **Inclusion criteria:** 18 years to 80 years old; acute corneal abrasion from mechanical trauma or removal of a foreign body by the physician **Exclusion criteria:** contact lenses wearer; previous corneal surgery or transplant; more than 36 hours after injury, contaminated or retained foreign body or eye infection; pregnancy; penetrating injury; immunosuppression; allergy to study medication; unable to attend follow-up; not fluent in English or Spanish; injury requiring urgent ophthalmologic evaluation (large or complicated abrasions with significant vision loss, corneal ulcers or lacerations) **Reported a subgroup analyses (Y/N):** no **Randomized (n):** 118 Tetracaine 0.5% group: 59 Artificial tear group: 59 **Exclusions and loss to follow-up (n; reasons):** 7; did not attend 24- to 48-hour follow-up in ED Tetracaine 0.5% group: 3 Artificial tear group: 4 **Analyzed (n):** 111 Artificial tear group: 55 Tetracaine 0.5% group: 56 **Age (median, IQR):** overall not reported Tetracaine 0.5% group: 35 (28 to 43) Artificial tear group: 38 (27 to 47) **Gender (number, % female):** 48, 41% Tetracaine 0.5% group: 23, 39% Artificial tear group: 25, 42% **Race/ethnicity (study definition, n, %):** not reported **Etiology of corneal abrasion (study definition, n, %):** metallic foreign body (13, 11%); other foreign body (32, 27%); direct trauma (31, 26%); unknown (42, 36%) Tetracaine 0.5% group: metallic foreign body (8, 14%); other foreign body (17, 29%); direct trauma (11, 17%); unknown (23, 40%) Artificial tear group: metallic foreign body (5, 9%); other foreign body (15, 25%); direct trauma (20, 34%); unknown (19, 32%) **Baseline pain (0 to 10 scale, median, IQR):** overall not reported Tetracaine 0.5% group: 7 (6 to 7.5) Artificial tear group: 7 (6 to 8)

Shipman 2021 *(Continued)*

Interventions	**Intervention:** tetracaine hydrochloride 0.5%, 1 drop every 30 minutes as needed up to 24 hours, dispensed in a single 2 mL bottle **Comparison:** artificial tears (Systane, Alcon), 1 drop every 30 minutes as needed up to 24 hours, dispensed in 4 x 0.5 mL ampules **Co-interventions:** • Polymyxin B sulfate/ trimethoprim sulfate, 2 drops every 4 hours up to 24 hours • Oral hydrocodone 7.5 mg/acetaminophen 325 mg, 1 to 2 tablets as needed every 6 hours for breakthrough pain
Outcomes	**Primary study outcome(s):** 1. Overall numeric rating scale (NRS) at 24- to 48-hour follow-up, assessed before and 2 minutes after applying study drop. The NRS scale is a 10 cm VAS (0 meaning no pain, 10 meaning worst pain) **Secondary study outcome(s):** 1. Overall NRS at 1 week follow-up NRS (0 to 10 cm scale; 0 meaning no pain, 10 meaning worst pain)* 2. Number of hydrocodone tablets taken at 48 hours 3. Number of study drops used 4. Residual corneal abrasion on slit lamp examination at 48 hours 5. Self-reported persistent symptoms at 1 week, by phone call if participant missed the 1-week ophthalmology follow-up 6. Repeated visits to any health professional that were related to their initial corneal abrasion assessed by phone interview at 1 week and chart review at study conclusion **Adverse event(s):** adverse events at 1 week **Measurement time points:** baseline (ED, visit 1), 24 to 48 hours (ED, visit 2), 1 week (Ophthalmology, visit 3), chart review of all participants at study conclusion *Secondary outcome in trial registration NCT04187417 but not reported in the published article (Shipman 2021)
Notes	**Sponsorship source:** "The study was funded in part by a grant from the Foundation of Osteopathic Emergency Medicine Young Investigator Award" **Conflicts of interest:** "no such relationships exist" **Informed consent obtained?:** yes **Ethics approval obtained?:** yes **Investigator's name:** Stacia Shipman **Affiliated institution:** Department of Emergency Medicine, INTEGRIS Southwest Medical Center, Oklahoma City, OK **Trial registration ID:** NCT04187417

Ting 2009

Study characteristics	
Methods	**Study design:** parallel RCT **Unit of randomization:** individual (1 eye included) **Study start date:** 2 May 2006 (anticipated date on trial registry; ACTRN012605000273684) **Study end date:** 2 May 2007 (calculated based on the reported duration of study) **Participant follow-up time:** 2 weeks **Treatment time:** 36 to 48 hours **Time from abrasion to randomization (hours):** less than 36 hours; the mean hours from injury in the tetracaine group was 13.8 hours and 15.8 hours in the saline group **Power calculation:** power and sample size calculations were based on a two-tailed difference of 25% to 50%, as there has been a large variation in corneal healing rates in previous studies

Ting 2009 *(Continued)*

Participants	**Country/countries:** Australia **Setting:** emergency department of an urban hospital **Inclusion criteria:** traumatic superficial corneal abrasion with or without a retained foreign body, or keratitis from welding flash exposure **Exclusion criteria:** over 36 hours since corneal injury, under 18 years old, known adverse reaction to study medications, eye disease other than refractive error, contact lens use, pregnant or lactating, eye infection, functionally one-eyed, requires urgent referral to ophthalmology (penetrating eye injury) **Reported a subgroup analysis (Y/N):** no **Randomized (n):** 47 Tetracaine 0.4% group: 22 Saline group: 25 **Exclusions and loss to follow-up (n; reasons):** 31; did not attend follow-up (22); retained foreign body/rust (2); data collected outside of follow-up window (7) Tetracaine 0.4% group: 15; did not attend follow-up (11); retained foreign body/rust (1); data collected outside of follow-up window (3) Saline group: 16; did not attend follow-up (11); retained foreign body/rust (1); data collected outside of follow-up window (4) **Analyzed (n):** 16 Tetracaine 0.4% group: 7 Saline group: 9 **Age (mean):** overall not reported Tetracaine 0.4% group: 35.1 Saline group: 33.6 **Gender (number, % female):** 0 (0%) **Race/ethnicity (study definition, n, %):** not reported **Etiology of corneal abrasion (study definition, n, %):** corneal abrasion (15, 32%), corneal foreign body (20, 43%), welding flash burn (10, 21%), welding flash burn and corneal foreign body (2, 4%) Tetracaine 0.4% group: corneal abrasion (8, 36%), corneal foreign body (9, 41%), welding flash burn (4, 18%), welding flash burn and corneal foreign body (1, 5%) Saline group: corneal abrasion (7, 28%), corneal foreign body (11, 44%), welding flash burn (6, 24%), welding flash burn and corneal foreign body (1, 4%) **Baseline pain (study scale):** not reported
Interventions	**Intervention:** amethocaine (tetracaine) 0.4%, 1 drop hourly as needed **Comparison:** normal saline 0.9%, 1 drop hourly as needed **Co-interventions:** 1. Oral analgesics (unspecified) as needed for eye pain 2. Topical antibiotics (unspecified)* *Not all participants received antibiotics. Discharged with topical antibiotics for subset of participants (8/22 amethocaine; 8/18 saline group)
Outcomes	**Primary study outcome(s):** 1. Proportions of patients whose cornea had completely re-epithelialized at 36 to 48 hours, defined as the absence of fluoresceine staining uptake **Secondary study outcome(s):** 1. Pain was measured using a VAS on an ungraded 100 mm horizontal line with the left end indicating “No pain” and the right end “Worst pain imaginable.” Pain assessed every 3 hours over 36 hours (up to 12 pain measurements) 2. Satisfaction with treatment received 3. Use of oral analgesia 4. Unscheduled medical review 5. Visual problems **Adverse event(s):** significant functional or clinical adverse

Ting 2009 *(Continued)*

	Measurement time points: baseline, 36- to 48-hour ED visit, 2-week telephone interview
Notes	**Sponsorship source:** listed source of support listed differs between reports. Funding source name: Mater Foundation in trial registry (ACTRN012605000273684); no source of support reported in the full-text publication (Ting 2009) **Conflicts of interest:** "none" declared **Informed consent obtained?:** yes **Ethics approval obtained?:** yes **Investigator's name:** Joseph Ting **Affiliated institution:** Department of Emergency Medicine, Mater Adults' Hospital, South Brisbane, Australia **Trial registration ID:** ACTRN012605000273684

Verma 1995

Study characteristics	
Methods	**Study design:** parallel RCT **Unit of randomization:** individual (whether one or both eyes were included in the analysis was unclear) **Study start date:** not reported **Study end date:** not reported **Participant follow-up time:** 6 months; pain scores were recorded for the first 4 days **Treatment time:** 24 hours **Time from abrasion to randomization (hours):** 0 **Power calculation:** "A total of 44 patients were recruited, which was deemed an appropriate sample size to give statistically significant results."
Participants	**Country/countries:** UK **Setting:** ophthalmology surgery **Inclusion criteria:** mean refraction diopters (D) at -3.00 ± 1.00 or at -6.00 ± 1.00, astigmatism (D) < −1.5, visual acuity > 20/30, age > 24 years **Reported subgroups (if applicable):** by mean preoperative refractive error. Group 1: Mean preoperative refractive error of -3.00 D (range, −2.75 to -4.00 D; 22 patients, 16 women and 6 men; age range, 26 to 54 years). Group 2: -6.00 D (range, -5.75 to -8.62 D; 22 patients, 13 women and 9 men; age range, 25 to 72 years) **Randomized (n):** 44 Tetracaine 1% group: 22 Physiologic saline group: 22 **Exclusions and loss to follow-up (n):** not reported **Exclusion reasons:** not reported **Analyzed (n):** not reported **Age (mean ± SD, range):** range 25 to 72 years, not reported by group **Gender (number, % female):** 29 (66 %), not reported by group **Race/ethnicity (study definition, n, %):** not reported **Etiology of corneal abrasion (study definition, n, %):** PRK (44, 100%) **Baseline pain (study scale):** not reported
Interventions	**Intervention:** tetracaine 1% without preservatives, 1 drop every 30 minutes during waking hours over 24 hours, dispensed 4 containers (40 drops) **Comparison:** physiologic saline, 1 drop every 30 minutes during waking hours over 24 hours, dispensed 4 containers (40 drops) **Co-interventions:** 1. Oral co-proxamol, 2 tablets every 8 hours over 2 days 2. Topical chloramphenicol 0.5%, 1 drop every 6 hours, over 1 week

Verma 1995 *(Continued)*

	Other treatments: preoperative: 1 drop of 4% pilocarpine and 4 drops of 1% tetracaine instilled onto the cornea. Immediate postoperative: patients received mydriatic drops (2% homatropine and 10% phenylephrine)
Outcomes	**Primary study outcome(s):** 1. Pain: VAS pain charts consisted of a series of horizontal lines 10 cm in length with "no pain" written at one end and "worst pain imaginable" at the other. Over 4 days, participants recorded their pain scores initially at 15-minute intervals for 1 hour, then, when awake, every 2 hours for 24 hours, and finally every 8 hours for 3 days 2. Epithelial healing: retro illumination photography; high-resolution digitized camera on slit lamp, photographs were taken at 24-hour intervals until full epithelial closure was noted. A subgroup had more frequent images 3. Refraction: refraction/best-corrected visual acuity 4. Visual function: self-reported vision function (e.g. night vision), objective measurements of haze, glare, and halo 5. Subjective surface quality: self-reported symptoms (e.g. blurred vision, gritty sensation, epithelial disturbance) 6. Objective surface quality: corneal topography, epithelial disturbances, and central irregularities retinoscopy, topography, slit lamp examination, tonometry, and full mydriatic fundoscopy **Secondary study outcome(s):** 1. Epithelial healing, 2. Visual acuity and function **Adverse event(s):** objective and subjective measurements of haze, glare, or halo; alteration in night vision postoperatively **Measurement time points:** baseline, daily until corneal full closure, subsequently at 1 week, and at 1, 3, and 6 months
Notes	**Sponsorship source:** "Iris Fund for the Prevention of Blindness research fellowship (Dr. Verma); Dr. Corbett received the Williams fellowship for medical and scientific research of the University of London, London, England. Prof. Marshall is a consultant to Summit Technology." **Conflicts of interest:** "Prof. Marshall is a consultant to Summit Technology" **Informed consent obtained?:** yes **Ethics approval obtained?:** yes **Investigator's name:** Seema Verma **Affiliated institution:** Department of Ophthalmology, St. Thomas' Hospital, London UK **Trial registration ID:** not reported

Waldman 2014

Study characteristics	
Methods	**Study design:** parallel RCT **Unit of randomization:** individual (1 eye per person included in study) **Study start date:** 1 November 2011 **Study end date:** 31 October 2012 **Participant follow-up time:** 1 month (telephone check) **Treatment time:** 24 hours **Time from abrasion to randomization (hours**): less than 36 hours **Power calculation:** “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%

Waldman 2014 *(Continued)*

	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."
Participants	**Country/countries:** New Zealand **Setting:** emergency department **Inclusion criteria:** presented to emergency within 36 hours of injury, simple acute corneal abrasions from mechanical trauma, ultraviolet light, foreign body, or from removal of foreign body by the physician **Exclusion criteria:** under 18 years old (one 17-year-old patient enrolled with parental consent), previous eye surgery or cataracts, wear contact lenses, injured both eyes, infectious or chemical conjunctivitis, grossly contaminated foreign body, ocular infection, allergic to study drugs, injury requiring urgent ophthalmologic evaluation (e.g. penetrating eye injuries, large or complicated corneal abrasions, or injuries causing a significant disruption of vision), deaf*, were unable to attend follow-up in 48 hours* **Reported a subgroup analyses (Y/N):** no **Randomized (n):** 122 Tetracaine 1% group: 61 Saline group: 61 **Exclusions and loss to follow-up (n; reasons):** 29; subsequently removed due to incorrect enrollment (n = 6, conjunctivitis (n = 2), chronic defect from eye surgery (n = 1), and large corneal lacerations (n = 3)). Excluded due to retained rust rings (n = 23) Tetracaine 1% group: 14; subsequently removed due to incorrect enrollment (n = 4). Excluded due to retained rust rings (n = 10) Saline group: 15; subsequently removed due to incorrect enrollment (n = 2). Excluded due to retained rust rings (n = 13) **Analyzed (n):** 93 Tetracaine 1% group: 47 Saline group: 46 **Age (median, range):** overall not reported Tetracaine 1% group: 37 (17 to 72) Saline group: 38 (19 to 74) **Gender (number, % female):** 12 (10%) Tetracaine 1% group: 4 (6.8%) Saline group: 8 (14%) **Race/ethnicity (study definition, n, %):** not reported **Etiology of corneal abrasion (study definition, n, %):** metallic foreign body (60, 51.7%), dirt foreign body (6, 5.2%), dust foreign body (15, 12.9%), wood foreign body (7, 6.0%), direct trauma (15, 12.9%), ultraviolet (3, 2.6%), unknown (8, 6.9%), other (2, 1.7%) Tetracaine 1% group: metallic foreign body (30, 50.8%), dirt foreign body (1, 1.7%), dust foreign body (7, 11.9%), wood foreign body (5, 8.5%), direct trauma (8, 13.6%), ultraviolet (3, 5.1%), unknown (5, 5.8%), other (0, 0%) Saline group: metallic foreign body (30, 52.6%), dirt foreign body (5, 8.8%), dust foreign body (8, 14.0%), wood foreign body (2, 3.5%), direct trauma (7, 12.3%), ultraviolet (0, 0%), unknown (3, 3.5%), other (3, 3.5%) **Baseline pain (study scale; median, range):** overall not reported Tetracaine 1% group: 0 to 100mm VAS; 48.0 mm (0 to 96 mm) Saline group: 0 to 100 mm VAS; 54.6 mm (10 to 98 mm) *Exclusion not in trial registration (ACTRN12611000448943); exclusion added in published report (Waldman 2014)
Interventions	**Intervention:** preservative-free tetracaine hydrochloride 1%, taken as often as every 30 minutes for 24 hours, dispensed 1.5 mL (3 x 0.5 mL commercially available vials; approximately 50 drops total)* **Comparison:** saline 0.9%, taken as often as every 30 minutes for 24 hours, dispensed 5 mL (one, single-use plastic bullet) **Co-interventions** • Topical preservative-free chloramphenicol antibiotics 1% • Paracetamol 500 mg, 2 tablets taken at specific times over 24 hours (08:00 hours, 12:00 hours, 16:00 hours, 20:00 hours)

Waldman 2014 *(Continued)*

	*Trial registration specified 2 x 0.5 mL minims, approximately 30 drops (ACTRN12611000448943); 1.5 mL, approximately 50 drops in published report (Waldman 2014)
Outcomes	**Primary study outcome(s):** 1. Corneal healing, adequate healing is defined as a lack of fluorescein uptake on slit lamp examination and absence of complications, assessed at the 48-hour follow-up 2. Visual acuity assessed at the 48-hour follow-up 3. Treatment effectiveness based on numeric rating scale (NRS) from 0 to 10 (higher values indicating more effectiveness) at 1 week and 1 month telephone follow-up 4. Return to normal vision question at 1 week and 1 month telephone follow-up 5. Participant-reported complications at 1 week and 1 month telephone follow-up **Secondary study outcome(s):** 1. Pain measured on a 100 mm VAS every 30 minutes for the first 2 hours after leaving the Emergency Department and then every 2 hours for the next 48 hours while awake **Adverse event(s):** delayed healing, enlarged abrasion, recurrent corneal ulceration, toxic keratitis, surface keratopathy, corneal storm infiltration, *Candidal* and bacterial keratitis, or uveitis **Measurement time points**: baseline, 48-hour Emergency Department follow-up, 1 week and 1 month telephone interview follow-up
Notes	**Sponsorship source:** "There was no funding for the study, no sponsorship or involvement with the drug manufacturer, or other financial support." **Conflicts of interest:** "The authors have no conflicts of interest to report." **Informed consent obtained?:** yes **Ethics approval obtained?:** yes **Investigator's name:** Neil Waldman **Affiliated institution:** Emergency Department, Quality Risk and Education Unit, Southland Hospital, Invercargill, New Zealand **Trial registration ID:** ACTRN12611000448943 **Trial discontinued:** "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." **Contacted authors:** study authors provided raw data for VAS pain scores at 24 hours and 48 hours

BCLs: bandage contact lenses
CI: confidence interval
D: diopters
ED: emergency department
ITT: intention-to-treat
IV: inverse variance
IQR: interquartile range
MD: mean difference
M-H: Mantel-Haenszel
NSAID: nonsteroidal anti-inflammatory drug
NRS: numeric rating scale
OR: odds ratio
PRK: photorefractive keratectomy
RCT: randomized controlled trial
RR: risk ratio
SD: standard deviation
SE: standard error
SMD: standardized mean difference
VAS: visual analog scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahmed 2001	Ineligible population: trial excluded participants with epithelial defects
Badalà 2004	Ineligible intervention: no amide or ester anesthetic
Carruthers 1995	Ineligible population: no participants with corneal abrasion
Castrén 1963	Ineligible population and indication: participants under 18 years old, anesthetic used for foreign body removal
Chatziralli 2010	Ineligible population: pre-operative participants only
Cherry 1996	Ineligible study design: non-randomized trial
Ferreira 1992	Ineligible population: pre-operative participants only
Filippone 1967	Ineligible population: no participants with corneal abrasion
Henrotte 1972	Ineligible study design: case series
Kirwan 2008	Ineligible intervention: anesthetics only administered once following surgery
NCT02483897	Ineligible study: withdrawn because of "inability to recruit at required rate"; we confirmed with the investigators that no data were available
NCT02771392	Ineligible study: trial never started and there was no enrollment; we confirmed with the investigators
NCT04283331	Ineligible intervention: impregnated bandage soft contact lens, no topical anesthetic
Steiner 1966	Ineligible population: randomized intervention study on animal models
Verma 1997	Ineligible comparison: no non-amide or non-ester control group
Weindler 2001	Ineligible population: pre-operative participants only

Characteristics of studies awaiting classification *[ordered by study ID]*

Aseff 1997

Methods	**Study design:** not reported **Unit of randomization:** not reported **Study start date:** not reported **Study end date:** not reported **Participant follow-up time:** 3 days **Treatment time:** not reported **Time from abrasion to randomization (hours)**: 0 **Power calculation:** not reported
Participants	**Country/countries:** Mexico **Setting:** ophthalmology surgery **Randomized (n):** 60 eyes **Exclusions and loss to follow-up (n):** not reported

Aseff 1997 *(Continued)*

	Exclusion reasons: not reported **Analyzed (n):** not reported **Age (mean ± SD, range):** not reported **Gender (number, % female):** not reported **Race/ethnicity (study definition, n, %):** not reported **Etiology of corneal abrasion (study definition, n, %):** not reported **Baseline pain:** not reported **Inclusion criteria:** not reported **Exclusion criteria:** not reported **Reported a subgroup analysis (Y/N):** not reported
Interventions	**Intervention:** tetracaine **Comparison:** diclofenac
Outcomes	**Primary study outcome(s):** 1. Pain/discomfort 2. Percent of re-epithelialization at 24 and 72 hours **Secondary study outcome(s):** not reported **Adverse event(s):** not reported **Measurement time points:** 24 and 72 hours
Notes	**Sponsorship source:** not reported **Conflicts of interest:** not reported **Informed consent obtained?:** yes **Ethics approval obtained?:** yes **Investigator's name:** Aseff A **Affiliated institution:** Department of Ophthalmology, Instituto Tecnologico y de Estudios Superiores de Monterrey-Hospital San Jose, Monterrey, NL **Address:** Monterrey, NL, Mexico **Trial registration ID:** not reported **Notes:** we could not confirm the study design with the authors despite several attempts to contact them

RISK OF BIAS

Legend: ✓ Low risk of bias ✗ High risk of bias ~ Some concerns

Risk of bias for analysis 1.2 Change in participant-reported ocular pain from baseline to 48 hours

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.2.1 Anesthetic vs placebo, VAS (0 to 10), post-surgery						
Verma 1995	✓	~	✓	✓	✓	~
Subgroup 1.2.2 Anesthetic vs placebo, VAS (0 to 10), post-trauma						

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Shipman 2021	✓	✓	✓	✓	✗	✗

Risk of bias for analysis 1.7 Proportion of participants with complications at furthest time point

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.7.1 At 1 week, post-surgery						
Verma 1995	✓	✓	✓	✓	✓	✓
Subgroup 1.7.2 At 1 to 2 weeks, post-trauma						
Ting 2009	✓	✓	✗	~	~	✗
Shipman 2021	✓	✓	✗	✓	~	✗
Waldman 2014	✓	~	✓	✗	✗	✗

Risk of bias for analysis 1.8 Proportion of participants with complications at furthest time point (RD) - subgroup by abrasion type

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.8.1 Post-surgery						
Oksuz 2006	~	✓	✗	✗	~	✗
Lim 1999	~	~	✓	~	~	~
Verma 1995	✓	✓	✓	✓	✓	✓
Subgroup 1.8.2 Post-trauma						

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Ting 2009	✓	✓	✗	~	~	✗
Ball 2010	✓	✗	~	✓	✓	✗
Shipman 2021	✓	✓	✗	✓	~	✗
Waldman 2014	✓	~	✓	✗	✗	✗

Risk of bias for analysis 2.3 Proportion of participants with complications at furthest time point (RD)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Lim 1999	~	~	✓	~	~	~

DATA AND ANALYSES

Comparison 1. Anesthetic vs placebo or NSAID

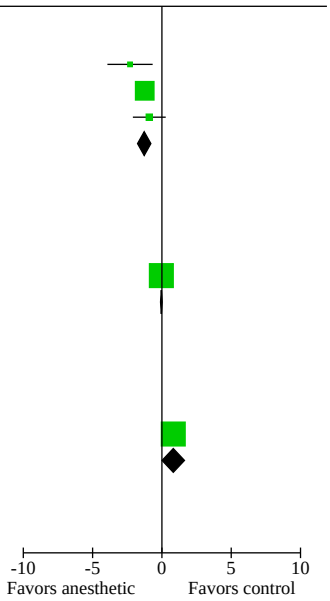
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Change in participant-reported ocular pain from baseline to 24 hours	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1.1 Anesthetic vs placebo, VAS (0 to 10), post-surgery	3	119	Mean Difference (IV, Random, 95% CI)	-1.28 [-1.76, -0.80]
1.1.2 Anesthetic vs placebo, VAS (0 to 10), post-trauma	1	76	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.10, 0.02]
1.1.3 Anesthetic vs NSAID, VAS (0 to 10), post-surgery	1	74	Mean Difference (IV, Random, 95% CI)	0.82 [0.01, 1.63]
1.2 Change in participant-reported ocular pain from baseline to 48 hours	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.1 Anesthetic vs placebo, VAS (0 to 10), post-surgery	1	44	Mean Difference (IV, Fixed, 95% CI)	0.41 [-0.45, 1.27]
1.2.2 Anesthetic vs placebo, VAS (0 to 10), post-trauma	1	111	Mean Difference (IV, Fixed, 95% CI)	-5.68 [-6.38, -4.98]
1.3 Change in participant-reported ocular pain from baseline to 72 hours	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.4 Proportion of post-trauma participants without complete resolution of epithelial defects by 24 to 72 hours - subgroup by tetracaine concentration	3	221	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.78, 2.42]
1.4.1 Tetracaine 0.4%	1	16	Risk Ratio (M-H, Random, 95% CI)	2.57 [0.29, 22.93]
1.4.2 Tetracaine 0.5%	1	112	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.65, 4.27]
1.4.3 Tetracaine 1%	1	93	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.53, 2.39]
1.5 Proportion of participants without complete resolution of epithelial defects by 24 to 72 hours	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.5.1 24 to 48 hours, post-trauma	3	221	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.78, 2.42]
1.5.2 48 hours or longer, post-surgery	1	30	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.55]
1.6 Proportion of participants without complete resolution of epithelial defects by 24 to 72 hours - subgroup by duration of use (RD)	5		Risk Difference (M-H, Random, 95% CI)	Subtotals only
1.6.1 24 to 48 hours, post-trauma	3	221	Risk Difference (M-H, Random, 95% CI)	0.06 [-0.04, 0.16]
1.6.2 24 to 48 hours, post-surgery	1	44	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.08, 0.08]
1.6.3 48 hours or longer, post-surgery	1	30	Risk Difference (M-H, Random, 95% CI)	-0.20 [-0.42, 0.02]
1.7 Proportion of participants with complications at furthest time point	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.7.1 At 1 week, post-surgery	1	44	Risk Ratio (M-H, Random, 95% CI)	7.00 [0.38, 128.02]
1.7.2 At 1 to 2 weeks, post-trauma	3	242	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.23, 5.46]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.8 Proportion of participants with complications at furthest time point (RD) - subgroup by abrasion type	7	394	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.03, 0.05]
1.8.1 Post-surgery	3	119	Risk Difference (M-H, Random, 95% CI)	0.03 [-0.06, 0.11]
1.8.2 Post-trauma	4	275	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.06, 0.06]

Analysis 1.1. Comparison 1: Anesthetic vs placebo or NSAID, Outcome 1: Change in participant-reported ocular pain from baseline to 24 hours

Study or Subgroup	Anesthetic Mean	Anesthetic SD	Anesthetic Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 Anesthetic vs placebo, VAS (0 to 10), post-surgery								
Lim 1999 (1)	5.78	2.28	15	8.08	2.28	15	8.6%	-2.30 [-3.93 , -0.67]
Oksuz 2006 (2)	2.39	0.89	23	3.63	1	22	75.0%	-1.24 [-1.79 , -0.69]
Verma 1995 (3)	1.47	2.19	22	2.38	1.8	22	16.4%	-0.91 [-2.09 , 0.27]
Subtotal (95% CI)			**60**			**59**	**100.0%**	**-1.28 [-1.76 , -0.80]**
Heterogeneity: Tau² = 0.00; Chi² = 1.90, df = 2 (P = 0.39); I² = 0%								
Test for overall effect: Z = 5.22 (P < 0.00001)								
1.1.2 Anesthetic vs placebo, VAS (0 to 10), post-trauma								
Waldman 2014 (4)	0.07	0.13	38	0.11	0.13	38	100.0%	-0.04 [-0.10 , 0.02]
Subtotal (95% CI)			**38**			**38**	**100.0%**	**-0.04 [-0.10 , 0.02]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.34 (P = 0.18)								
1.1.3 Anesthetic vs NSAID, VAS (0 to 10), post-surgery								
Montard 1999 (5)	2.91	1.77	38	2.09	1.77	36	100.0%	0.82 [0.01 , 1.63]
Subtotal (95% CI)			**38**			**36**	**100.0%**	**0.82 [0.01 , 1.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.99 (P = 0.05)								
Test for subgroup differences: Chi² = 0.00, df = 2 (P < 0.00001), I² = 0%								

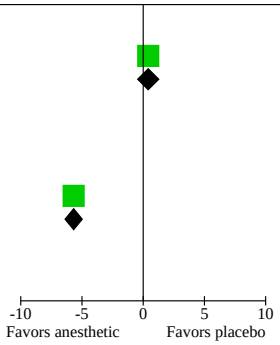


Footnotes

(1) At day 1, proparacaine 0.05%, SD from reported P values
(2) At 10 hours, lidocaine 2%
(3) At 24 hours, tetracaine 1%
(4) At 24 hours, tetracaine 1%, converted VAS scores (original scale 0 to 100), individual level data provided by the author team
(5) Average over 24 hours, tetracaine 1% versus diclofenac 0.1%, imputed SD from reported P value of 0.05

Analysis 1.2. Comparison 1: Anesthetic vs placebo or NSAID, Outcome 2: Change in participant-reported ocular pain from baseline to 48 hours

Study or Subgroup	Anesthetic Mean	Anesthetic SD	Anesthetic Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 Anesthetic vs placebo, VAS (0 to 10), post-surgery								
Verma 1995 (1)	1.22	1.46	22	0.81	1.46	22	100.0%	0.41 [-0.45 , 1.27]
Subtotal (95% CI)			**22**			**22**	**100.0%**	**0.41 [-0.45 , 1.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.93 (P = 0.35)								
1.2.2 Anesthetic vs placebo, VAS (0 to 10), post-trauma								
Shipman 2021 (2)	1.55	1.83	56	7.23	1.95	55	100.0%	-5.68 [-6.38 , -4.98]
Subtotal (95% CI)			**56**			**55**	**100.0%**	**-5.68 [-6.38 , -4.98]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 15.82 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%								



Footnotes

(1) At 48 hours, tetracaine 1%

(2) At 24 to 48 hours, tetracaine 0.5%

Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions

(C) Bias due to missing outcome data

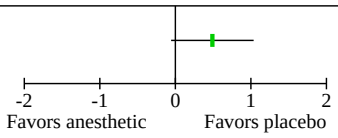
(D) Bias in measurement of the outcome

(E) Bias in selection of the reported result

(F) Overall bias

Analysis 1.3. Comparison 1: Anesthetic vs placebo or NSAID, Outcome 3: Change in participant-reported ocular pain from baseline to 72 hours

Study or Subgroup	Anesthetic Mean	Anesthetic SD	Anesthetic Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI
Verma 1995 (1)	0.69	1.01	22	0.2	0.83	22	0.49 [-0.06 , 1.04]

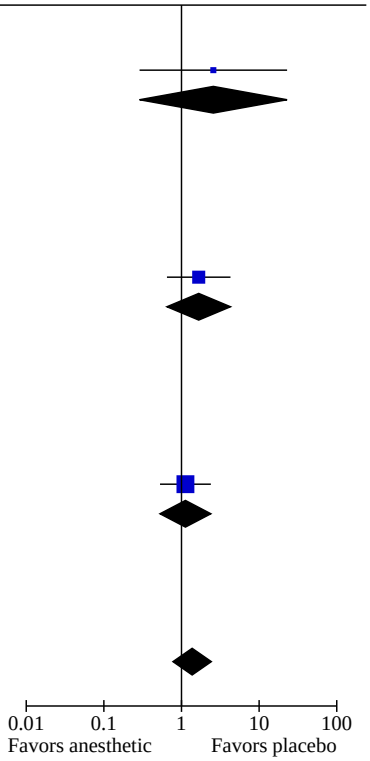


Footnotes

(1) At 64 hours, tetracaine 1%, data extracted from figure

Analysis 1.4. Comparison 1: Anesthetic vs placebo or NSAID, Outcome 4: Proportion of post-trauma participants without complete resolution of epithelial defects by 24 to 72 hours - subgroup by tetracaine concentration

Study or Subgroup	Anesthetic Events	Anesthetic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Tetracaine 0.4%						
Ting 2009 (1)	2	7	1	9	6.7%	2.57 [0.29 , 22.93]
Subtotal (95% CI)		**7**		**9**	**6.7%**	**2.57 [0.29 , 22.93]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.40)						
1.4.2 Tetracaine 0.5%						
Shipman 2021 (2)	10	56	6	56	36.4%	1.67 [0.65 , 4.27]
Subtotal (95% CI)		**56**		**56**	**36.4%**	**1.67 [0.65 , 4.27]**
Total events:	10		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
1.4.3 Tetracaine 1%						
Waldman 2014 (3)	11	46	10	47	56.8%	1.12 [0.53 , 2.39]
Subtotal (95% CI)		**46**		**47**	**56.8%**	**1.12 [0.53 , 2.39]**
Total events:	11		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.30 (P = 0.76)						
Total (95% CI)		**109**		**112**	**100.0%**	**1.37 [0.78 , 2.42]**
Total events:	23		17			
Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 2 (P = 0.69); I² = 0%						
Test for overall effect: Z = 1.09 (P = 0.28)						
Test for subgroup differences: Chi² = 0.75, df = 2 (P = 0.69), I² = 0%						

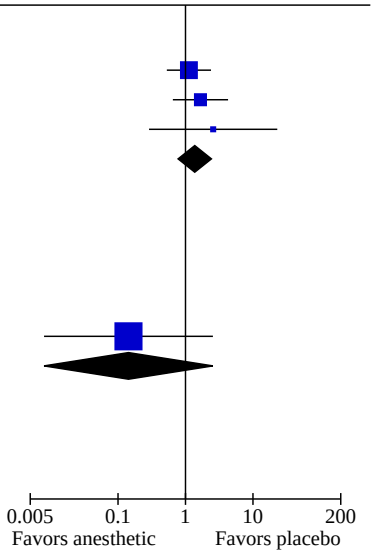


Footnotes

(1) At 36 to 48 hours
(2) At 24 to 48 hours
(3) At 48 hours

Analysis 1.5. Comparison 1: Anesthetic vs placebo or NSAID, Outcome 5: Proportion of participants without complete resolution of epithelial defects by 24 to 72 hours

Study or Subgroup	Anesthetic Events	Anesthetic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 24 to 48 hours, post-trauma						
Waldman 2014 (1)	11	46	10	47	56.8%	1.12 [0.53 , 2.39]
Shipman 2021 (2)	10	56	6	56	36.4%	1.67 [0.65 , 4.27]
Ting 2009 (3)	2	7	1	9	6.7%	2.57 [0.29 , 22.93]
Subtotal (95% CI)		**109**		**112**	**100.0%**	**1.37 [0.78 , 2.42]**
Total events:	23		17			
Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 2 (P = 0.69); I² = 0%						
Test for overall effect: Z = 1.09 (P = 0.28)						
1.5.2 48 hours or longer, post-surgery						
Lim 1999 (4)	0	15	3	15	100.0%	0.14 [0.01 , 2.55]
Subtotal (95% CI)		**15**		**15**	**100.0%**	**0.14 [0.01 , 2.55]**
Total events:	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.32 (P = 0.19)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%						

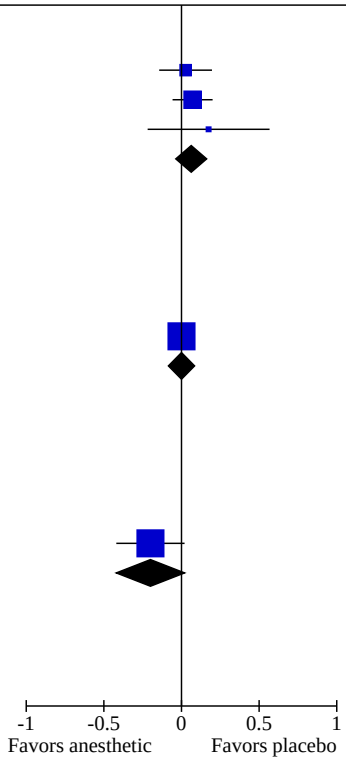


Footnotes

(1) At 48 hours, tetracaine 1%
(2) At 24 to 48 hours, tetracaine 0.5%
(3) At 36 to 48 hours, tetracaine 0.4%
(4) At 72 hours, proparacaine 0.05%

Analysis 1.6. Comparison 1: Anesthetic vs placebo or NSAID, Outcome 6: Proportion of participants without complete resolution of epithelial defects by 24 to 72 hours - subgroup by duration of use (RD)

Study or Subgroup	Anesthetic Events	Anesthetic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
1.6.1 24 to 48 hours, post-trauma						
Waldman 2014 (1)	11	46	10	47	34.2%	0.03 [-0.14 , 0.20]
Shipman 2021 (2)	10	56	6	56	59.4%	0.07 [-0.06 , 0.20]
Ting 2009 (3)	2	7	1	9	6.4%	0.17 [-0.22 , 0.57]
Subtotal (95% CI)		**109**		**112**	**100.0%**	**0.06 [-0.04 , 0.16]**
Total events:	23		17			
Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 2 (P = 0.78); I² = 0%						
Test for overall effect: Z = 1.24 (P = 0.22)						
1.6.2 24 to 48 hours, post-surgery						
Verma 1995 (4)	0	22	0	22	100.0%	0.00 [-0.08 , 0.08]
Subtotal (95% CI)		**22**		**22**	**100.0%**	**0.00 [-0.08 , 0.08]**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
1.6.3 48 hours or longer, post-surgery						
Lim 1999 (5)	0	15	3	15	100.0%	-0.20 [-0.42 , 0.02]
Subtotal (95% CI)		**15**		**15**	**100.0%**	**-0.20 [-0.42 , 0.02]**
Total events:	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.78 (P = 0.07)						

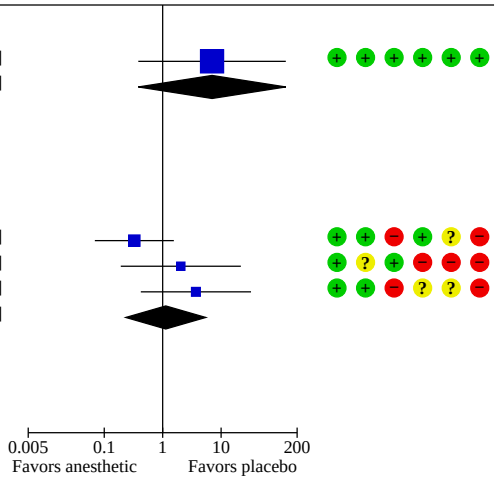


Footnotes

(1) At 48 hours, tetracaine 1%
(2) At 24 to 48 hours, tetracaine 0.5%
(3) At 36 to 48 hours, tetracaine 0.4%
(4) At 72 hours, tetracaine 1%
(5) At 72 hours, proparacaine 0.05%

Analysis 1.7. Comparison 1: Anesthetic vs placebo or NSAID, Outcome 7: Proportion of participants with complications at furthest time point

Study or Subgroup	Anesthetic Events	Anesthetic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 At 1 week, post-surgery						
Verma 1995 (1)	3	22	0	22	100.0%	7.00 [0.38 , 128.02]
Subtotal (95% CI)		**22**		**22**	**100.0%**	**7.00 [0.38 , 128.02]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						
1.7.2 At 1 to 2 weeks, post-trauma						
Shipman 2021 (2)	2	56	6	55	42.2%	0.33 [0.07 , 1.55]
Waldman 2014 (1)	2	46	1	47	27.4%	2.04 [0.19 , 21.77]
Ting 2009 (3)	3	17	1	21	30.4%	3.71 [0.42 , 32.49]
Subtotal (95% CI)		**119**		**123**	**100.0%**	**1.13 [0.23 , 5.46]**
Total events:	7		8			
Heterogeneity: Tau² = 0.90; Chi² = 3.71, df = 2 (P = 0.16); I² = 46%						
Test for overall effect: Z = 0.15 (P = 0.88)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%						



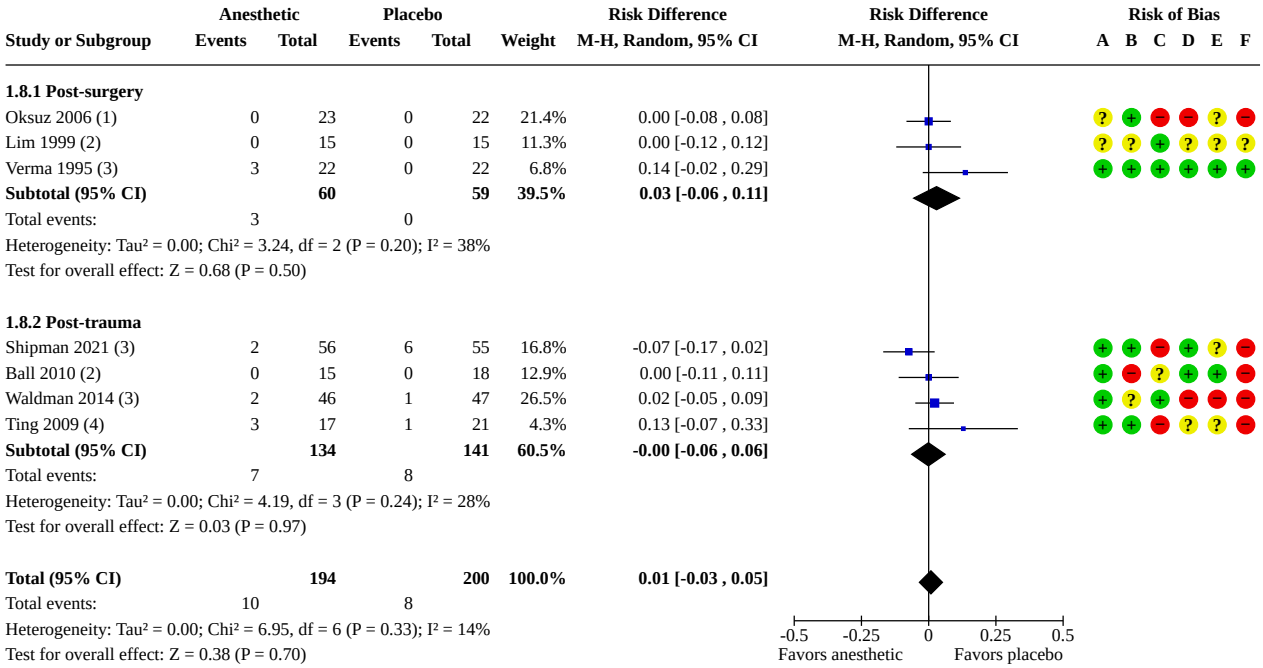
Footnotes

(1) At 1 week, tetracaine 1%
(2) At 1 week, tetracaine 0.5%
(3) At 2 weeks, tetracaine 0.4%

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.8. Comparison 1: Anesthetic vs placebo or NSAID, Outcome 8: Proportion of participants with complications at furthest time point (RD) - subgroup by abrasion type



Footnotes

(1) At 48 hours, lidocaine 2%
(2) At 1 week, proparacaine 0.05%
(3) At 1 week, tetracaine 1%
(4) At 2 weeks, tetracaine 0.4%

Risk of bias legend

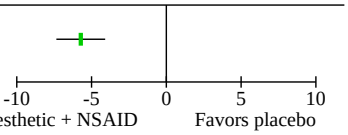
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 2. Anesthetic + NSAID vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Change in participant-reported ocular pain from baseline to 24 hours	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.2 Proportion of participants without complete resolution of epithelial defects by 24 to 72 hours	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.3 Proportion of participants with complications at furthest time point (RD)	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: Anesthetic + NSAID vs placebo, Outcome 1: Change in participant-reported ocular pain from baseline to 24 hours

Study or Subgroup	Anesthetic + NSAID Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Lim 1999 (1)	2.36	2.28	15	8.08	2.28	15	-5.72 [-7.35 , -4.09]

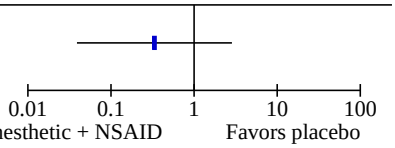


Footnotes

(1) At day 1, proparacaine 0.05% + diclofenac 0.1%, SD from reported P values

Analysis 2.2. Comparison 2: Anesthetic + NSAID vs placebo, Outcome 2: Proportion of participants without complete resolution of epithelial defects by 24 to 72 hours

Study or Subgroup	Anesthetic + NSAID Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI
Lim 1999 (1)	1	15	3	15	0.33 [0.04 , 2.85]

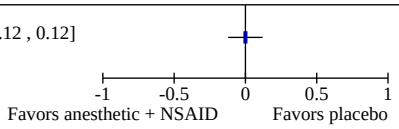


Footnotes

(1) At 72 hours, proparacaine 0.05% + diclofenac 0.1%

Analysis 2.3. Comparison 2: Anesthetic + NSAID vs placebo, Outcome 3: Proportion of participants with complications at furthest time point (RD)

Study or Subgroup	Anesthetic + NSAID Events	Total	Placebo Events	Total	Risk Difference M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Lim 1999 (1)	0	15	0	15	0.00 [-0.12 , 0.12]	?	?	+	?	?	?



Footnotes

(1) At 1 week, proparacaine 0.05% plus 0.1% diclofenac

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

ADDITIONAL TABLES

Table 1. Study characteristics

Study ID	Country	Etiology	Intervention(s)	Comparison(s)	Co-intervention(s)	No. participants randomized/analyzed, intervention arm	No. participants randomized/analyzed, control arm	Intervention duration	Note
Ball 2010	Canada	Trauma	Proparacaine 0.05% 2 to 4 drops, as needed, for 7 days, max dispensed 40 mL	Saline drops (color and smell-matched)	AB: gatifloxacin, 1 drop every 2 hours, for 7 days OA: 325 mg acetaminophen with 30 mg of codeine, 1 to 2 tablets every 4 hours if needed, for 7 days	NR/15	NR/18	1 week	—
Lim 1999	South Korea	PRK	1) Proparacaine 0.05% 2) Diclofenac 0.1% + proparacaine 0.05% 1 drop every 4 hours for 7 days	Artificial tears (Tears Natural) 1 drop every 4 hours for 7 days	AB: ofloxacine, every 6 hours, for 1 week OA: mefenamic acid, as needed	1) 15/15 2) 15/15	15/15	1 week	3 of 7 treatment arms
Montard 1999	France	PRK	Tetracaine 1% every 30 minutes for 24 hours	Diclofenac 0.1% every 4 hours for 3 days	AB: ofloxacine, every 6 hours, for 1 week OA: mefenamic acid, as needed Other: BCLs	38/NR	36/NR	24 hours	—
Oksuz 2006	Turkey	Pterygium	Lidocaine 2%[c] 1 mL every hour for 3 hours, starting 1 hour postop	Artificial tears[c] (Thilo-Tears Jelly) 1 mL every hour for 3 hours, starting 1 hour postop	AB: NR OA: none Other: patched	23/NR	22/NR	3 hours	—
Shahinian 1997	Canada and US	PRK	Proparacaine 0.05% 1 drop 4 times a day for 1 week	Artificial tears (Hypotears) 1 drop 4 times a day for 1 week	AB: 0.3% tobramycin and 0.1% dexamethasone, 4 times a day, over 1 week OA: acetaminophen and hydrocodone bitartrate, as needed, over 1 week	25 eyes/25 eyes	23 eyes/23 eyes	1 week	—

Table 1. Study characteristics *(Continued)*

					Topical: topical diclofenac 0.1%, 4 times a day, for the first 48 hours Other: BCLs				
Shipman 2021	US	Trauma	Tetracaine 0.5% 1 drop every 30 minutes as needed for 24 hours, max dispensed 2 mL	Artificial tears (Systane) 1 drop every 30 minutes as needed for 24 hours, max dispensed 2 mL	AB: polymyxin B sulfate/trimethoprim sulfate, 2 drops every 4 hours, max 24 hours OA: hydrocodone 7.5 mg/acetaminophen 325 mg, 1 to 2 tablets as needed every 6 hours, max 12 tablets	59/56	59/55	24 hours	—
Ting 2009	Australia	Trauma	Tetracaine 0.4% 1 drop every hour as needed for 48 hours	Saline drops 0.9% 1 drop every hour as needed for 48 hours	AB: topical antibiotics (unspecified)[a] OA: oral analgesics (unspecified) as needed for eye pain	22/7	25/9	36 to 48 hours	—
Verma 1995	UK	PRK	Tetracaine 1%[d] 1 drop every 30 minutes during waking hours for 24 hours, max dispensed 40 drops	Saline drops[d] (physiologic saline) 1 drop every 30 minutes during waking hours for 24 hours, max dispensed 40 drops	AB: chloramphenicol 0.5%, topical, 1 drop every 6 hours, over 1 week OA: co-proxamol, 2 tablets every 8 hours, over 2 days[b]	22/NR	22/NR	24 hours	—
Waldman 2014	New Zealand	Trauma	Tetracaine 1% as needed, up to every 30 minutes for 24 hours, max dispensed 1.5 mL (50 drops)	Saline drops 0.9% as needed, up to every 30 minutes for 24 hours, max dispensed 1.5 mL (50 drops)	AB: preservative-free chloramphenicol antibiotics 1%, topical ointment OA: paracetamol 500 mg, 2 tablets at 08:00, 12:00, 16:00, 20:00, oral, over 24 hours[b]	61/47	61/46	24 hours	—

AB: topical antibiotics; **BCLs:** bandage contact lenses; **NR:** not reported; **OA:** oral anesthetic; **PRK:** photorefractive keratectomy
[a]Not all participants received antibiotics (8/22 participants in the tetracaine group and 8/18 in the saline group received antibiotics).
[b]The study prescribed oral anesthetic to prevent breakthrough pain.
[c]Prescribed at 1, 2, and 3 hours postop, inpatient setting. Not taken on an as-needed basis.
[d]Prescribed at a specific schedule. Not taken on an as-needed basis.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Cornea] explode all trees
#2 MeSH descriptor: [Corneal Diseases] explode all trees
#3 MeSH descriptor: [Epithelium, Corneal] explode all trees
#4 MeSH descriptor: [Keratectomy] explode all trees
#5 MeSH descriptor: [Refractive Surgical Procedures] explode all trees
#6 cornea*
#7 (ocular NEXT/1 (surface* or epithelia*)) or keratectom* or keratoplast* or "cross linking"
#8 MeSH descriptor: [Eye Injuries] explode all trees
#9 Eye* NEXT/3 (injur* or abrasion* or erosion* or trauma* or wound* or (foreign NEXT/1 bod*) or (epithelial NEXT/1 defect*) or lesion* or laceration or surger* or surgical)
#10 {OR #1-#9}
#11 MeSH descriptor: [Amides] explode all trees
#12 MeSH descriptor: [Esters] explode all trees
#13 amide OR amides OR ester OR esters
#14 topical NEXT/2 (analgesic* or anesthetic* or anaesthetic*)
#15 MeSH descriptor: [Tetracaine] explode all trees
#16 "ak-t-caine" OR amethocaine OR ametocaine OR ametop OR anetaine OR anethaine OR butethanol OR butethol OR contralgin OR curtacaine OR decicain OR decicaine OR "dextrose-pontocaine hcl" OR dicain OR dicaine OR fissucain OR gingicain OR intercain OR landocaine OR laudocaine OR meethobalm OR mucaesthin OR niphanoid OR pantocain OR pantocaine OR pontocaine OR rexocaine OR tetocaine OR tetracain OR tetracaine OR tetrakain OR tetrracaine OR tonexol OR uromucaesthin OR "136-47-0" OR "94-24-6"
#17 alcaine OR anestalcon OR "chibro-kerakain" OR kainair OR keracaine OR miraxil OR "ocu-caine" OR oftetic OR ophthaine OR ophthetic OR opthetic OR "poen-caina" OR proparacain OR proparacaine OR proporacaine OR proxymetacaine OR "499-67-2" OR "5875-06-9"
#18 MeSH descriptor: [Lidocaine] explode all trees
#19 akten OR "algrx 3268" OR algrx3268 OR alphacaine OR anestacaine OR anestacon OR anestacone OR aritmal OR betacaine OR cidancaina OR "col 1077" OR col1077 OR "corus 1030" OR corus1030 OR dalcaine OR dentipatch OR dolicaine OR duncaine OR dynexan OR "ela-max" OR esracain OR esracaine OR farmacaina OR "gesicain jelly" OR "gesicain ointment" OR "gesicain viscous" OR glydo OR gravocain OR isicaine OR jetocaine OR jetokain OR "l-caine" OR lecasin OR leostesin OR "lida mantle" OR lidbree OR lidocain OR lidocaine OR lidocaton OR lidocor OR lidocorit OR lidoderm OR lidonest OR lidopain OR lidopen OR lidorx OR lidothesin OR lignocaine OR lignostab OR lincaine OR liquocaine OR liris OR "ll 30" OR ll30 OR "lmx 4" OR "lmx 5" OR "lta ii kit" OR maricaine OR "neo novutox" OR neolidocaton OR Octocaine OR otipax OR "paediatric lta kit" OR "pediatric lta kit" OR penles OR radiaguard OR ralvo OR "remicaine gel" OR roxicaina OR rucaina OR ruciana OR solarcaine OR solcaine OR "sp 103" OR sp103 OR truxacaine OR "uad caine" OR vasocaine OR versatis OR xidocaine OR xilina OR xiline OR xilocaina OR "xilonest pomade" OR "xilotane gel" OR xilyne OR xylcaine OR xylestesin OR Xylesthesin OR xylocain OR xylocaina OR xylocaine OR xylocard OR xylocitin OR xyloctin OR xyloneural OR xylonor OR "xyloproct n" OR xyloton OR xylotox OR xylyne OR zingo OR ztlido OR "137-58-6" OR "24847-67-4" OR "56934-02-2" OR "73-78-9"
#20 Oxybuprocaine OR benoxil OR benoxinate OR cebesine OR conjucain OR conjuncain OR dorsacain OR dorsacaine OR lacrimin OR novesin OR novesine OR oxibuprocainum OR oxibuprokain OR oxybucaine OR prescaina OR "5987-82-6" OR "99-43-4"
#21 MeSH descriptor: [Cocaine] this term only
#22 Cocaine OR cocain OR codrenine OR erythroxylin OR goprelto OR locosthetic OR neurocaine OR numbrino OR sterilocaine OR "50-36-2" OR "53-21-4" OR "5937-29-1"
#23 {OR #11-#22}
#24 #10 AND #23 in Trials

Appendix 2. MEDLINE Ovid search strategy

1. Randomized Controlled Trial.pt.
2. Controlled Clinical Trial.pt.
3. (randomized or randomised).ab,ti.
4. placebo.ab,ti.
5. drug therapy.fs.
6. randomly.ab,ti.
7. trial.ab,ti.
8. groups.ab,ti.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp animals/ not humans.sh.
11. 9 not 10
12. exp Cornea/
13. exp Corneal Diseases/
14. exp Epithelium, Corneal/

15. exp Keratectomy/
16. exp Refractive Surgical Procedures/
17. cornea*.tw.
18. ((ocular adj1 (surface* or epithelia*)) or keratectom* or keratoplast* or "cross linking").tw.
19. exp eye injuries/
20. (Eye* adj3 (injur* or abrasion* or erosion* or trauma* or wound* or foreign bod* or "epithelial defect*" or lesion* or laceration or surger* or surgical)).tw.
21. or/12-20
22. exp Amides/
23. exp Esters/
24. (amide or amides or ester or esters).tw.
25. (topical adj2 (analgesic* or anesthetic* or anaesthetic*)).tw.
26. exp Tetracaine/
27. ("ak-t-caine" or amethocaine or ametocaine or ametop or anetaine or anethaine or butethanol or butethol or contralgin or curtacaine or decicain or decicaine or "dextrose-pontocaine hcl" or dicain or dicaine or fissucain or gingicain or intercain or landocaine or laudocaine or meethobalm or mucaesthin or niphanoid or pantocain or pantocaine or pontocaine or rexocaine or tetocaine or tetracain or tetracaine or tetrakain or tetrracaine or tonexol or uromucaesthin or "136-47-0" or "94-24-6").tw,rn.
28. (alcaine or anestalcon or "chibro-kerakain" or kainair or keracaine or miraxil or "ocu-caine" or oftetic or ophthaine or ophthetic or opthetic or "poen-caina" or proparacain or proparacaine or proporacaine or proxymetacaine or "499-67-2" or "5875-06-9").tw,rn.
29. exp Lidocaine/
30. (akten or "algrx 3268" or algrx3268 or alphacaine or anestacaine or anestacon or anestacone or aritmal or betacaine or cidancaina or "col 1077" or col1077 or "corus 1030" or corus1030 or dalcaine or dentipatch or dolicaine or duncaine or dynexan or "ela-max" or esracain or esracaine or farmacaina or "gesicain jelly" or "gesicain ointment" or "gesicain viscous" or glydo or gravocain or isicaine or jetocaine or jetokain or "l-caine" or lecasin or leostesin or "lida mantle" or lidbree or lidocain or lidocaine or lidocaton or lidocor or lidocorit or lidoderm or lidonest or lidopain or lidopen or lidorx or lidothesin or lignocaine or lignostab or lincaine or liquocaine or liris or "ll 30" or ll30 or "lmx 4" or "lmx 5" or "lta ii kit" or maricaine or "neo novutox" or neolidocaton or Octocaine or otipax or "paediatric lta kit" or "pediatric lta kit" or penles or radiaguard or ralvo or "remicaine gel" or roxicaina or rucaina or ruciana or solarcaine or solcaine or "sp 103" or sp103 or truxacaine or "uad caine" or vasocaine or versatis or xidocaine or xilina or xiline or xilocaina or "xilonest pomade" or "xilotane gel" or xilyne or xylcaine or xylestesin or Xylesthesin or xylocain or xylocaina or xylocaine or xylocard or xylocitin or xyloctin or xyloneural or xylonor or "xyloproct n" or xyloton or xylotox or xylyne or zingo or ztlido or "137-58-6" or "24847-67-4" or "56934-02-2" or "73-78-9").tw,rn.
31. (Oxybuprocaine or benoxil or benoxinate or cebesine or conjucain or conjuncain or dorsacain or dorsacaine or lacrimin or novesin or novesine or oxibuprocainum or oxibuprokain or oxybucaine or prescaina or "5987-82-6" or "99-43-4").tw,rn.
32. cocaine/
33. (Cocaine or cocain or codrenine or erythroxylin or goprelto or locosthetic or neurocaine or numbrino or sterilocaine or "50-36-2" or "53-21-4" or "5937-29-1").tw,rn.
34. or/22-33
35. 21 and 34
36. 11 and 35

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville (Glanville 2006).

Appendix 3. Embase.com search strategy

#1 'randomized controlled trial'/exp
#2 'randomization'/exp
#3 'double blind procedure'/exp
#4 'single blind procedure'/exp
#5 random*:ab,ti
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 'animal'/exp OR 'animal experiment'/exp
#8 'human'/exp
#9 #7 AND #8
#10 #7 NOT #9
#11 #6 NOT #10
#12 'clinical trial'/exp
#13 (clin* NEAR/3 trial*):ab,ti
#14 ((singl* OR doubl* OR trebl* OR tripl*) NEAR/3 (blind* OR mask*)):ab,ti
#15 'placebo'/exp
#16 placebo*:ab,ti
#17 random*:ab,ti
#18 'experimental design'/exp
#19 'crossover procedure'/exp

#20 'control group'/exp
#21 'latin square design'/exp
#22 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23 #22 NOT #10
#24 #23 NOT #11
#25 'comparative study'/exp
#26 'evaluation'/exp
#27 'prospective study'/exp
#28 control*:ab,ti OR prospectiv*:ab,ti OR volunteer*:ab,ti
#29 #25 OR #26 OR #27 OR #28
#30 #29 NOT #10
#31 #30 NOT (#11 OR #23)
#32 #11 OR #24 OR #31
#33 'cornea'/exp
#34 'cornea disease'/exp
#35 'cornea epithelium'/exp
#36 'cornea surgery'/exp
#37 'refractive surgery'/exp
#38 Cornea*:ab,ti,kw
#39 (ocular NEXT/1 (surface* or epithelia*)):ab,ti,kw or (keratectom* or keratoplast* or "cross linking"):ab,ti,kw
#40 'eye injury'/exp
#41 (Eye* NEXT/3 (injur* or abrasion* or erosion* or trauma* or wound* or "foreign bod*" or "epithelial defect*" or lesion* or laceration or surger* or surgical)):ab,ti,kw
#42 #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41
#43 'amide'/exp
#44 'ester'/exp
#45 (amide OR amides OR ester OR esters):ab,ti,kw
#46 'tetracaine'/exp
#47 ("ak-t-caine" OR amethocaine OR ametocaine OR ametop OR anetaine OR anethaine OR butethanol OR butethol OR contralgin OR curtacaine OR decicain OR decicaine OR "dextrose-pontocaine hcl" OR dicain OR dicaine OR fissucain OR gingicain OR intercain OR landocaine OR laudocaine OR meethobalm OR mucaesthin OR niphanoid OR pantocain OR pantocaine OR pontocaine OR rexocaine OR tetocaine OR tetracain OR tetracaine OR tetrakain OR tetrracaine OR tonexol OR uromucaesthin OR "136-47-0" OR "94-24-6"):ab,ti,kw,tn
#48 'proxymetacaine'/exp
#49 (alcaine OR anestalcon OR "chibro-kerakain" OR kainair OR keracaine OR miraxil OR "ocu-caine" OR oftetic OR ophthaine OR ophthetic OR opthetic OR "poen-caina" OR proparacain OR proparacaine OR proporacaine OR proxymetacaine OR "499-67-2" OR "5875-06-9"):ab,ti,kw,tn
#50 'lidocaine'/exp
#51 (akten OR "algrx 3268" OR algrx3268 OR alphacaine OR anestacaine OR anestacon OR anestacone OR aritmal OR betacaine OR cidancaina OR "col 1077" OR col1077 OR "corus 1030" OR corus1030 OR dalcaine OR dentipatch OR dolicaine OR duncaine OR dynexan OR "ela-max" OR esracain OR esracaine OR farmacaina OR "gesicain jelly" OR "gesicain ointment" OR "gesicain viscous" OR glydo OR gravocain OR isicaine OR jetocaine OR jetokain OR "l-caine" OR lecasin OR leostesin OR "lida mantle" OR lidbree OR lidocain OR lidocaine OR lidocaton OR lidocor OR lidocorit OR lidoderm OR lidonest OR lidopain OR lidopen OR lidorx OR lidothesin OR lignocaine OR lignostab OR lincaine OR liquocaine OR liris OR "ll 30" OR ll30 OR "lmx 4" OR "lmx 5" OR "lta ii kit" OR maricaine OR "neo novutox" OR neolidocaton OR Octocaine OR otipax OR "paediatric lta kit" OR "pediatric lta kit" OR penles OR radiaguard OR ralvo OR "remicaine gel" OR roxicaina OR rucaina OR ruciana OR solarcaine OR solcaine OR "sp 103" OR sp103 OR truxacaine OR "uad caine" OR vasocaine OR versatis OR xidocaine OR xilina OR xiline OR xilocaina OR "xilonest pomade" OR "xilotane gel" OR xilyne OR xylcaine OR xylestesin OR Xylesthesin OR xylocain OR xylocaina OR xylocaine OR xylocard OR xylocitin OR xyloctin OR xyloneural OR xylonor OR "xyloproct n" OR xyloton OR xylotox OR xylyne OR zingo OR ztlido OR "137-58-6" OR "24847-67-4" OR "56934-02-2" OR "73-78-9"):ab,ti,kw,tn
#52 'oxybuprocaine'/exp
#53 (Oxybuprocaine OR benoxil OR benoxinate OR cebesine OR conjucain OR conjuncain OR dorsacain OR dorsacaine OR lacrimin OR novesin OR novesine OR oxibuprocainum OR oxibuprokain OR oxybucaine OR prescaina OR "5987-82-6" OR "99-43-4"):ab,ti,kw,tn
#54 'cocaine'/exp
#55 (Cocaine OR cocain OR codrenine OR erythroxylin OR goprelto OR locosthetic OR neurocaine OR numbrino OR sterilocaine OR "50-36-2" OR "53-21-4" OR "5937-29-1"):ab,ti,kw,tn
#56 #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55
#57 #42 AND #56
#58 #32 AND #57

Appendix 4. PubMed search strategy

#1 ((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomised[tiab] OR randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT (animals[mh] NOT humans[mh])

#2 cornea*[tw]
#3 (ocular[tw] AND (surface*[tw] OR epithelia*[tw])) OR keratectom*[tw] OR keratoplast*[tw] OR "cross linking"[tw]
#4 (eye[tw] OR eyes[tw] OR eyelid*[tw]) AND (injur*[tw] OR abrasion*[tw] OR erosion*[tw] OR trauma*[tw] OR wound*[tw] OR "foreign bod*"[tw] OR "epithelial defect*"[tw] OR lesion*[tw] OR laceration*[tw] OR surger*[tw] OR surgical[tw])
#5 #2 OR #3 OR #4
#6 (amide[tw] OR amides[tw] OR ester[tw] OR esters[tw])
#7 ("ak-t-caine"[tw] OR amethocaine[tw] OR ametocaine[tw] OR ametop[tw] OR anetaine[tw] OR anethaine[tw] OR butethanol[tw] OR butethol[tw] OR contralgin[tw] OR curtacaine[tw] OR decicain[tw] OR decicaine[tw] OR "dextrose-pontocaine hcl"[tw] OR dicain[tw] OR dicaine[tw] OR fissucain[tw] OR gingicain[tw] OR intercain[tw] OR landocaine[tw] OR laudocaine[tw] OR meethobalm[tw] OR mucaesthin[tw] OR niphanoid[tw] OR pantocain[tw] OR pantocaine[tw] OR pontocaine[tw] OR rexocaine[tw] OR tetocaine[tw] OR tetracain[tw] OR tetracaine[tw] OR tetrakain[tw] OR tetrracaine[tw] OR tonexol[tw] OR uromucaesthin[tw] OR "136-47-0"[tw] OR "94-24-6"[tw])
#8 (alcaine[tw] OR anestalcon[tw] OR "chibro-kerakain"[tw] OR kainair[tw] OR keracaine[tw] OR miraxil[tw] OR "ocu-caine"[tw] OR oftetic[tw] OR ophthaine[tw] OR ophthetic[tw] OR opthetic[tw] OR "poen-caina"[tw] OR proparacain[tw] OR proparacaine[tw] OR proporacaine[tw] OR proxymetacaine[tw] OR "499-67-2"[tw] OR "5875-06-9"[tw])
#9 (akten[tw] OR "algrx 3268"[tw] OR algrx3268[tw] OR alphacaine[tw] OR anestacaine[tw] OR anestacon[tw] OR anestacone[tw] OR aritmal[tw] OR betacaine[tw] OR cidancaina[tw] OR "col 1077"[tw] OR col1077[tw] OR "corus 1030"[tw] OR corus1030[tw] OR dalcaine[tw] OR dentipatch[tw] OR dolicaine[tw] OR duncaine[tw] OR dynexan[tw] OR "ela-max"[tw] OR esracain[tw] OR esracaine[tw] OR farmacaina[tw] OR "gesicain jelly"[tw] OR "gesicain ointment"[tw] OR "gesicain viscous"[tw] OR glydo[tw] OR gravocain[tw] OR isicaine[tw] OR jetocaine[tw] OR jetokain[tw] OR "l-caine"[tw] OR lecasin[tw] OR leostesin[tw] OR "lida mantle"[tw] OR lidbree[tw] OR lidocain[tw] OR lidocaine[tw] OR lidocaton[tw] OR lidocor[tw] OR lidocorit[tw] OR lidoderm[tw] OR lidonest[tw] OR lidopain[tw] OR lidopen[tw] OR lidorx[tw] OR lidothesin[tw] OR lignocaine[tw] OR lignostab[tw] OR lincaine[tw] OR liquocaine[tw] OR liris[tw] OR "ll 30"[tw] OR ll30[tw] OR "lmx 4"[tw] OR "lmx 5"[tw] OR "lta ii kit"[tw] OR maricaine[tw] OR "neo novutox"[tw] OR neolidocaton[tw] OR Octocaine[tw] OR otipax[tw] OR "paediatric lta kit"[tw] OR "pediatric lta kit"[tw] OR penles[tw] OR radiaguard[tw] OR ralvo[tw] OR "remicaine gel"[tw] OR roxicaina[tw] OR rucaina[tw] OR ruciana[tw] OR solarcaine[tw] OR solcaine[tw] OR "sp 103"[tw] OR sp103[tw] OR truxacaine[tw] OR "uad caine"[tw] OR vasocaine[tw] OR versatis[tw] OR xidocaine[tw] OR xilina[tw] OR xiline[tw] OR xilocaina[tw] OR "xilonest pomade"[tw] OR "xilotane gel"[tw] OR xilyne[tw] OR xylcaine[tw] OR xylestesin[tw] OR Xylesthesin[tw] OR xylocain[tw] OR xylocaina[tw] OR xylocaine[tw] OR xylocard[tw] OR xylocitin[tw] OR xyloctin[tw] OR xyloneural[tw] OR xylonor[tw] OR "xyloproct n"[tw] OR xyloton[tw] OR xylotox[tw] OR xylyne[tw] OR zingo[tw] OR ztlido[tw] OR "137-58-6"[tw] OR "24847-67-4"[tw] OR "56934-02-2"[tw] OR "73-78-9"[tw])
#10 oxybuprocaine[tw] OR benoxil[tw] OR benoxinate[tw] OR cebesine[tw] OR conjucain[tw] OR conjuncain[tw] OR dorsacain[tw] OR dorsacaine[tw] OR lacrimin[tw] OR novesin[tw] OR novesine[tw] OR oxibuprocainum[tw] OR oxibuprokain[tw] OR oxybucaine[tw] OR prescaina[tw] OR "5987-82-6"[tw] OR "99-43-4"[tw]
#11 cocaine[tw] OR cocain[tw] OR codrenine[tw] OR erythroxylin[tw] OR goprelto[tw] OR locosthetic[tw] OR neurocaine[tw] OR numbrino[tw] OR sterilocaine[tw] OR "50-36-2"[tw] OR "53-21-4"[tw] OR "5937-29-1"[tw]
#12 #6 OR #7 OR #8 OR #9 OR #10 OR #11
#13 #1 AND #5 AND #12
#14 Medline[sb]
#15 #13 NOT #14

Appendix 5. LILACS search strategy

(MH:A09.371.060.217$ OR MH:C11.204$ OR MH:A09.371.060.217.325$ OR MH:A10.272.510$ OR MH:E04.378$ OR MH:E04.540.825$ OR MH:C10.900.300.284.250$ OR MH:C11.297$ OR MH:C26.915.300.425.250$ OR cornea$ OR (ocular surface$) OR (epithelia$ surface$) OR keratectomy$ OR keratoplasty$ OR "cross linking" OR (Eye$ AND (injur$ OR abrasion$ OR erosion$ OR trauma$ OR wound$ OR "foreign body" OR "foreign bodies" OR "epithelial defect" OR lesion$ OR laceration OR surger$ OR surgical))) AND (Amides OR amidas OR MH:D02.065$ OR Esters OR esters OR MH:D02.241.400$ OR MH:SP4.097.036.654$ OR Tetracaine OR Tetracaina OR MH:D02.241.223.100.050.500.968$ OR MH: D02.455.426.559.389.127.020.937.968$ OR "ak-t-caine" OR amethocaine OR ametocaine OR ametop OR anetaine OR anethaine OR butethanol OR butethol OR contralgin OR curtacaine OR decicain OR decicaine OR "dextrose-pontocaine hcl" OR dicain OR dicaine OR fissucain OR gingicain OR intercain OR landocaine OR laudocaine OR meethobalm OR mucaesthin OR niphanoid OR pantocain OR pantocaine OR pontocaine OR rexocaine OR tetocaine OR tetracain OR tetracaine OR tetrakain OR tetrracaine OR tonexol OR uromucaesthin OR "136-47-0" OR "94-24-6" OR proparacaine OR alcaine OR anestalcon OR "chibro-kerakain" OR kainair OR keracaine OR miraxil OR "ocu-caine" OR oftetic OR ophthaine OR ophthetic OR opthetic OR "poen-caina" OR proparacain OR proporacaine OR proxymetacaine OR "499-67-2" OR "5875-06-9" OR Lidocaine OR Lidocaina OR MH:D02.065.199.092.500$ OR MH: D02.092.146.113.092.500$ OR akten OR "algrx 3268" OR algrx3268 OR alphacaine OR anestacaine OR anestacon OR anestacone OR aritmal OR betacaine OR cidancaina OR "col 1077" OR col1077 OR "corus 1030" OR corus1030 OR dalcaine OR dentipatch OR dolicaine OR duncaine OR dynexan OR "ela-max" OR esracain OR esracaine OR farmacaina OR "gesicain jelly" OR "gesicain ointment" OR "gesicain viscous" OR glydo OR gravocain OR isicaine OR jetocaine OR jetokain OR "l-caine" OR lecasin OR leostesin OR "lida mantle" OR lidbree OR lidocain OR lidocaine OR lidocaton OR lidocor OR lidocorit OR lidoderm OR lidonest OR lidopain OR lidopen OR lidorx OR lidothesin OR lignocaine OR lignostab OR lincaine OR liquocaine OR liris OR "ll 30" OR ll30 OR "lmx 4" OR "lmx 5" OR "lta ii kit" OR maricaine OR "neo novutox" OR neolidocaton OR Octocaine OR otipax OR "paediatric lta kit" OR "pediatric lta kit" OR penles OR radiaguard OR ralvo OR "remicaine gel" OR roxicaina OR rucaina OR ruciana OR solarcaine OR solcaine OR "sp 103" OR sp103 OR truxacaine OR "uad caine" OR vasocaine OR versatis OR xidocaine OR xilina OR xiline OR xilocaina OR "xilonest pomade" OR "xilotane gel" OR xilyne OR xylcaine OR xylestesin OR Xylesthesin OR xylocain OR

xylocaina OR xylocaine OR xylocard OR xylocitin OR xyloctin OR xyloneural OR xylonor OR "xyloproct n" OR xyloton OR xylotox OR xylyne OR zingo OR ztlido OR "137-58-6" OR "24847-67-4" OR "56934-02-2" OR "73-78-9" OR Oxybuprocaine OR benoxil OR benoxinate OR cebesine OR conjucain OR conjuncain OR dorsacain OR dorsacaine OR lacrimin OR novesin OR novesine OR oxibuprocainum OR oxibuprokain OR oxybucaine OR prescaina OR "5987-82-6" OR "99-43-4" OR Cocaine OR cocain OR codrenine OR erythroxylin OR goprelto OR locosthetic OR neurocaine OR numbrino OR sterilocaine OR "50-36-2" OR "53-21-4" OR "5937-29-1")

Appendix 6. ClinicalTrials.gov search strategy

((cornea OR corneal OR ocular surface OR ocular epithelial OR ocular epithelium OR keratectomy OR keratoplasty OR "cross linking") OR (eye AND (injury OR abrasion OR erosion OR trauma OR wound OR "foreign body" OR "epithelial defect" OR lesion OR laceration OR surgery OR surgical))) AND (Amide OR ester OR tetracaine OR proparacaine OR lidocaine OR oxybuprocaine OR cocaine)

Appendix 7. WHO ICTRP search strategy

corneal AND amide OR corneal AND ester OR corneal AND tetracaine OR corneal AND proparacaine OR corneal AND lidocaine OR corneal AND oxybuprocaine OR corneal AND cocaine

cornea AND amide OR cornea AND ester OR cornea AND tetracaine OR cornea AND proparacaine OR cornea AND lidocaine OR cornea AND oxybuprocaine OR cornea AND cocaine

eye injury AND amide OR eye injury AND ester OR eye injury AND tetracaine OR eye injury AND proparacaine OR eye injury AND lidocaine OR eye injury AND oxybuprocaine OR eye injury AND cocaine

ocular surface AND amide OR ocular surface AND ester OR ocular surface AND tetracaine OR ocular surface AND proparacaine OR ocular surface AND lidocaine OR ocular surface AND oxybuprocaine OR ocular surface AND cocaine

keratectomy AND amide OR keratectomy AND ester OR keratectomy AND tetracaine OR keratectomy AND proparacaine OR keratectomy AND lidocaine OR keratectomy AND oxybuprocaine OR keratectomy AND cocaine

keratoplasty AND amide OR keratoplasty AND ester OR keratoplasty AND tetracaine OR keratoplasty AND proparacaine OR keratoplasty AND lidocaine OR keratoplasty AND oxybuprocaine OR keratoplasty AND cocaine

WHAT'S NEW

Date	Event	Description
3 October 2023	Amended	Amendment to the Summary of Findings Table 1, Outcome: Proportion of participants without complete resolution of epithelial defect by 24-72 hours; Illustrative comparative risks (95% CI), Corresponding risk with anesthetic, Placebo, post-surgery. The error did not impact the data or review findings or interpretation. The review did not use illustrative risk in any other sections.

HISTORY

Protocol first published: Issue 5, 2022
Review first published: Issue 8, 2023

Date	Event	Description
10 February 2023	New search has been performed	The original search on 19 February 2022 led to nine included studies and one study 'awaiting classification'. A top-up search on 10 February 2023 yielded no new eligible studies.

CONTRIBUTIONS OF AUTHORS

All review authors contributed to the conception and design of the review, participated in study selection, data extraction, and/or analysis, drafted portions of the review, commented on drafts critically regarding intellectual content, and approved the final version for publication.

DECLARATIONS OF INTEREST

- **Michael Sulewski:** declared that he has no conflict of interest.
- **Cristos Ifantides:** reported ownership of stock in Pfizer and consulting fees from Alcon. His partner works for AbbVie, a manufacturer of eye medications, but the partner does not work in the eye care space.
- **Louis Leslie:** reported a grant from the National Eye Institute, National Institutes of Health, USA; payment to institution.
- **Kyongjin Cho:** declared that he has no conflict of interest.
- **Su-Hsun Liu:** reported a grant from the National Eye Institute, National Institutes of Health, USA; payment to institution.
- **Irene C Kuo:** reported consulting fees from Okogen (one-time discussion re: therapy/structuring trials for treatment of adenoviral conjunctivitis) and Novan (one-time phone conversation re: therapy for adenoviral conjunctivitis); personal payments.

SOURCES OF SUPPORT

Internal sources

- None, Other

  No internal source of support.

External sources

- National Eye Institute, National Institutes of Health, USA, USA

  Cochrane Eyes and Vision US Project, supported by grant UG1EY020522 (PI: Tianjing Li, MD, MHS, PhD)
- Queen's University Belfast, UK

  Gianni Virgili, Co-ordinating Editor for Cochrane Eyes and Vision's work, is funded by the Centre for Public Health, Queen's University of Belfast, Northern Ireland (ended in April 2023)
- Public Health Agency, UK

  The HSC Research and Development (R&D) Division of the Public Health Agency funds the Cochrane Eyes and Vision editorial base at Queen's University Belfast (ended in April 2023)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of interventions
We expanded the intervention to allow for comparisons of anesthetics plus a second topical treatment (NSAIDs) with control.

Measures of treatment effect
We also calculated the risk difference (RD) and 95% CI for dichotomous outcomes when an included study reported zero events in either comparison arm. We felt that the studies with zero events in both arms were informative, even if the baseline risk may differ across study populations.

Subgroup analysis

- Subgroup analysis by gender or race was not performed due to the lack of stratified data reported.
- Subgroup analysis by frequency of use (2 to 3 times versus ≥ 4 times per day) was not performed because all included trials examined the intervention with a dosing frequency at ≥ 4 times per day.

Summary of findings and assessment of the certainty of the evidence

- We reported both safety outcomes rather than choosing only one based on data availability because both outcomes are clinically important.
- We reported risks of adverse events per person, rather than per person-time as planned in the protocol because not all included trials reported itemized adverse events.
- We clarified the use of the study-level risk of bias assessment for GRADE using domains 1 to 3 of the RoB 2 tool in the methods section.

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics; *Anesthetics, Local; Anti-Inflammatory Agents, Non-Steroidal [therapeutic use]; *Corneal Injuries [drug therapy]; Pain, Postoperative

MeSH check words

Adolescent; Adult; Aged; Humans; Middle Aged; Young Adult