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Topical non-steroidal anti-inflammatory drugs for analgesia in traumatic corneal abrasions (Review)

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[Intervention Review]

Topical non-steroidal anti-inflammatory drugs for analgesia in traumatic corneal abrasions

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ABSTRACT

Background

Traumatic corneal abrasions are relatively common and there is a lack of consensus about analgesia in their management. It is therefore important to document the clinical efficacy and safety profile of topical ophthalmic non-steroidal anti-inflammatory drugs (NSAIDs) in the management of traumatic corneal abrasions.

Objectives

To identify and evaluate all randomised controlled trials (RCTs) comparing the use of topical NSAIDs with placebo or any alternative analgesic interventions in adults with traumatic corneal abrasions (including corneal abrasions arising from foreign body removal), to reduce pain, and its effects on healing time.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) (2017, Issue 2), MEDLINE Ovid (1946 to 30 March 2017), Embase Ovid (1947 to 30 March 2017), LILACS (Latin American and Caribbean Health Sciences Literature Database) (1982 to 30 March 2017), OpenGrey (System for Information on Grey Literature in Europe) (www.opengrey.eu/); searched 30 March 2017, ZETOC (1993 to 30 March 2017), the ISRCTN registry (www.isrctn.com/editAdvancedSearch); searched 30 March 2017, ClinicalTrials.gov (www.clinicaltrials.gov); searched 30 March 2017 and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en); searched 30 March 2017. We did not use any date or language restrictions in the electronic searches for trials.We checked the reference lists of identified trials to search for further potentially relevant studies.

Selection criteria

RCTs comparing topical NSAIDs to placebo or any alternative analgesic interventions in adults with traumatic corneal abrasions.

Data collection and analysis

Two review authors independently performed data extraction and assessed risks of bias in the included studies. We rated the certainty of the evidence using GRADE.

Main results

We included nine studies that met the inclusion criteria, reporting data on 637 participants.The studies took place in the UK, USA, Israel, Italy, France and Portugal. These studies compared five types of topical NSAIDs (0.1% indomethacin, 0.03% flurbiprofen, 0.5% ketorolac, 1% indomethacin, 0.1% diclofenac) to control (consisting of standard care and in four studies used placebo eye drops). Overall, the studies were at an unclear or high risk of bias (particularly selection and reporting bias). None of the included studies reported the primary outcome measures of this review, namely participant-reported pain intensity reduction of 30% or more or 50% or more at 24 hours. Four trials, that included data on 481 participants receiving NSAIDs or control (placebo/standard care), reported on the use of 'rescue' analgesia at 24 hours as a proxy measure of pain control. Topical NSAIDs were associated with a reduction in the need for oral analgesia compared with control (risk ratio (RR) 0.46, 95% confidence interval (CI) 0.34 to 0.61; low-certainty evidence). Approximately 4 out of 10 people in the control group used rescue analgesia at 24 hours. No data were available on the use of analgesia at 48 or 72 hours.

One trial (28 participants) reported on the proportion of abrasions healed after 24 and 48 hours. These outcomes were similar in both arms of the trial. (at 24 hours RR 1.00 (0.81 to 1.23); at 48 hours RR 1.00 (0.88 to 1.14); low-certainty evidence). In the control group nine out of 10 abrasions were healed within 24 hours and all were healed by 48 hours. Complications of corneal abrasions were reported in 6 studies (609 participants) and were infrequently reported (4 complications, 1 in NSAID groups (recurrent corneal erosion) and 3 in control groups (2 recurrent corneal erosions and 1 corneal abscess), very low-certainty evidence). Possible drug-related adverse events (AEs) were reported in two trials (163 participants), with the number of adverse events low (4 AEs, 3 in NSAID group, including discomfort/photophobia on instillation, conjunctival hyperaemia and urticaria, and 1 in the control group, corneal abscess) very low-certainty evidence.

Authors' conclusions

The findings of the included studies do not provide strong evidence to support the use of topical NSAIDs in traumatic corneal abrasions. This is important, since NSAIDs are associated with a higher cost compared to oral analgesics. None of the trials addressed our primary outcome measure of participant-reported pain intensity reduction of 30% or more or 50% or more at 24 hours.

PLAIN LANGUAGE SUMMARY

Topical non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of pain in traumatic corneal abrasions

What is the aim of this review?

The aim of this Cochrane Review was to find out if topical (applied directly to the surface of the eye) non-steroidal anti-inflammatory drugs (NSAIDs) for traumatic corneal abrasions reduce pain. Cochrane researchers collected and analysed all relevant studies to answer this question. We found nine studies.

Key messages

It is unclear if using topical NSAIDs is helpful in traumatic corneal abrasions. Topical NSAIDs cost more to use than alternative treatments such as oral pain-killing tablets.

What was studied in the review?

A corneal abrasion is a scratch on the cornea of the eye. The cornea is the clear window that is in front of the iris, which is the coloured part of the eye. The cornea is important both for vision and for protecting the eye. When a corneal abrasion occurs, it causes significant pain and discomfort. A traumatic corneal abrasion is a corneal abrasion caused by an injury, such as the eye being poked or something like dirt or sand being trapped under the eyelid and scratching the cornea.

NSAIDs are one form of pain management for people with corneal abrasions.They may reduce the pain.

What are the main results of the review?

The Cochrane researchers found nine relevant studies. Three studies each were from the UK and the USA, one from Italy, one from Israel and one from France/Portugal. These studies used five types of topical NSAIDs (0.1% indomethacin, 0.03% flurbiprofen, 0.5% ketorolac, 1% indomethacin, 0.1% diclofenac). The studies compared the topical NSAIDs with antibiotic eye drops, artificial tears, eye patching and dummy (placebo) eye drops. Three of the studies were funded by the manufacturer while the other six studies did not report their funding source.

The results of the review show that:

- It is unclear if people treated with topical NSAIDs experience a clinically meaningful reduction in pain compared with people being treated with placebo or standard care (antibiotic eye drops, artificial tears, eye patching) but they may use less oral pain killers.

- Where drug-related side effects, and complications of corneal abrasion (e.g. poor healing or infection) were reported (in two trials), the numbers were low.

How up-to-date is this review?

Cochrane researchers searched for studies that had been published up to March 2017.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Topical NSAIDs compared to control for analgesia in traumatic corneal abrasions

Patient or population: analgesia in traumatic corneal abrasions
Setting: hospital emergency departments
Intervention: topical NSAIDs
Comparison: placebo/standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo/ usual care	Risk with Topical NSAIDs				
Participant-reported pain intensity reduction of 30%/50% or greater at 24 hours	See comment	See comment	N/A	N/A	N/A	None of the included studies reported the primary outcome measures for this review
Use of rescue oral analgesia at 24 hours	400 per 1,000	184 per 1,000 (136 to 244)	RR 0.46 (0.34 to 0.61)	481 (4 RCTs)	⊕⊕◯◯ LOW[1]	-
Use of rescue oral analgesia at 48/72 hours	See comment	See comment	N/A	N/A	N/A	None of the included studies reported rescue analgesia at 48 hours or at 72 hours as an outcome measure
Proportion of abrasions healed after 24 hours	900 per 1,000	900 per 1,000 (729 to 1,000)	RR 1.00 (0.81 to 1.23)	28 (1 RCT)	⊕⊕◯◯ LOW[1]	-
Proportion of abrasions healed after 48 hours	1,000 per 1,000	1000 per 1,000 (880 to 1,000)	RR 1.00 (0.88 to 1.14)	28 (1 RCT)	⊕⊕◯◯ LOW[1]	-
Complications of corneal abrasion	10 per 1,000	4 per 1,000 (1 to 29)	RR 0.44 (0.07 to 2.96)	609 (6 RCTs)	⊕◯◯◯ VERY LOW[1,2]	-

Drug-related adverse events	10 per 1,000	30 per 1,000 (3 to 276)	RR 2.95 (0.32 to 27.60)	163 (2 RCTs)	⊕◯◯◯ VERY LOW[1,2]	-

*__The risk in the intervention group__ (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; **RR:** Risk ratio

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

[1]Downgraded two levels for limitations in study design and implementation
[2]Downgraded one level for imprecision (wide confidence intervals that cross the null effect)

BACKGROUND

Description of the condition

A corneal abrasion results from a disruption in the integrity of the corneal epithelium and generally results from physical external forces scraping the corneal surface (Wilson 2004). Traumatic corneal abrasions are very common ophthalmic injuries and represent a significant healthcare burden to general emergency departments (EDs), ophthalmology emergency departments and General Practitioners (Chiapella 1985; Edwards 1987; Fenton 2001; Shields 1991). In one study, ophthalmic emergencies accounted for 6.1% of all ED attendances at a district general hospital over a 12-month period; 65% of these were trauma-related, of which 24% were corneal abrasions (Edwards 1987). Traumatic corneal abrasions also represent a significant economic burden on society in general. For example, in the USA, corneal abrasions account for approximately 15% of all work-related eye diseases that cause missed time from work (Harris 2008).

A traumatic corneal abrasion is also associated with significant patient morbidity. Its diagnosis is suggested by a history of recent ocular trauma (usually unilateral) and subsequent acute pain, tearing, photophobia, foreign body sensation, with or without effects on visual acuity (blurred vision). Other symptoms include: pain with extraocular muscle movement, blepharospasm and headache. Deeper scratches can cause corneal scarring that can impair vision to the point where corneal transplantation is needed. Recurrent corneal erosion may follow corneal trauma and can produce disabling ocular symptoms and predispose the cornea to infection (Watson 2013).

Description of the intervention

Although current treatment recommendations for traumatic corneal abrasions stress the use of topical antibiotics and topical (ophthalmic) or oral analgesics (Wilson 2004), there is no universal consensus regarding corneal abrasion management (Sabri 1998). Routine use of topical anaesthetics is not recommended, due to recognised corneal complications associated with their use (Pharmakakis 2002; Yagci 2011). Most corneal abrasions heal with the use of topical antibiotics (drops or ointment) and analgesics (topical (ophthalmic) or oral). Regarding management of the pain associated with corneal abrasions, topical ophthalmic non-steroidal anti-inflammatory drugs (NSAIDs) have demonstrable efficacy, particularly where potential opioid-induced sedation is intolerable (Weaver 2003). However, there is also no consensus regarding management of the pain caused by traumatic corneal abrasions. A national survey of 470 members of the Canadian Association of Emergency Physicians revealed wide variation in pain management preferences for traumatic corneal abrasions; these included oral analgesics (82.1%), cycloplegics (65.1%) and topical NSAIDs (52.8%) (Calder 2004).

There have been scattered reports of adverse effects, including corneal melting, associated with topical NSAIDs, particularly after cataract surgery, concurrent use of topical steroids and prolonged administration (Guidera 2001; Lin 2000). A previous systematic review of the use of the topical NSAIDs for corneal abrasions failed to perform a meta-analysis of adverse effects due to insufficient data (Calder 2005).

How the intervention might work

Topical NSAID use results in a clinically significant decrease in pain (by an average of 1.3 cms on a standard 10-cm pain scale), a decrease in oral analgesic use and a decrease in requirement for narcotic analgesia (Weaver 2003). Topical NSAID use has been shown to be associated with earlier return to work after a traumatic corneal abrasion (Kaiser 1997).

Why it is important to do this review

The use of topical NSAIDs for the management of pain in traumatic corneal abrasions is a clinically valid topic for a Cochrane Review for many reasons. Firstly, corneal abrasions are relatively common. Secondly, they are associated with significant morbidity, healthcare costs and societal economic burden. Thirdly, there is a lack of consensus regarding analgesia in traumatic corneal abrasions. Fourthly, as the use of topical ophthalmic NSAIDs is very common, it is important to document any incidence of adverse effects when used in the management of traumatic corneal abrasions. Furthermore, a Cochrane Review that is continuously updated as new evidence is published may lead to clinical practice guidelines which may improve the efficiency and quality of patient care (Edwards 1987; Fenton 2001; Thyagarajan 2006). Moreover, the last non-Cochrane systematic review on this topic was published almost twelve years ago (Calder 2005). This Cochrane Review aims to synthesise the current best evidence, which will be continuously updated as relevant new trials are published, regarding the role of topical NSAIDs for analgesia in traumatic corneal abrasions (including corneal abrasions arising from foreign body removal).

OBJECTIVES

To identify and evaluate all randomised controlled trials (RCTs) comparing the use of topical NSAIDs with placebo or any alternative analgesic interventions in adults with traumatic corneal abrasions (including corneal abrasions arising from foreign body removal) to reduce pain, and its effects on healing time.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs in all languages. A RCT was defined as a study in which participants were allocated to treatment groups on the basis of a method to generate a random sequence (for example, using random-number tables).

We did not include studies with cross-over designs because these are not appropriate designs for the clinical condition of interest in this review and for this research question.

Types of participants

We included adults aged 18 and over with traumatic corneal abrasion(s) (including corneal abrasions arising from foreign body removal).

Types of interventions

The target intervention was topical NSAIDs (dose as defined by study authors, either overall daily dose or number of drops per day) in adults with traumatic corneal abrasions (including corneal abrasions arising from foreign body removal), compared to the following interventions:

1. Administration of cycloplegics (e.g. cyclopentolate drops, homatropine drops).
2. Administration of oral analgesics (e.g. NSAIDs, opioids, paracetamol/acetaminophen).
3. Administration of ocular lubricants (e.g. artificial tears (hydrogels)).
4. Administration of topical antibiotics (e.g. chloramphenicol, fusidic acid, trimethoprim/polymyxin).
5. Eye patching.

Types of outcome measures

Primary outcomes

1. Participant-reported pain intensity reduction of 30% or more at 24 hours (dichotomous data).
2. Participant-reported pain intensity reduction of 50% or more at 24 hours (dichotomous data).

Secondary outcomes

1. Use of 'rescue' analgesia (i.e. oral analgesia) at 24 hours, 48 hours and 72 hours.
2. Percentage/proportion healed after 24 and 48 hours (healing should have been ascertained using fluorescein staining or slit-lamp examination).
3. Complications of corneal abrasion (e.g. corneal ulceration, corneal infections, recurrent corneal erosion syndrome) as defined by the study authors.
4. Whether the use of concurrent topical antibiotics (drops or ointments) with additional lubricating effects reduced pain.

Adverse effects (severe, minor)

We looked for the following adverse effects:

1. Drug-related adverse events (e.g. corneal melting, corneal scarring, allergic conjunctivitis or keratitis secondary to ocular medications).
2. Other adverse events as defined by the study authors.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist conducted systematic searches in the following databases for randomised controlled trials and controlled clinical trials. There were no language or publication year restrictions. The date of the search was 30 March 2017.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 2) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 30 March 2017) (Appendix 1);
- MEDLINE Ovid (1946 to 30 March 2017) (Appendix 2);
- Embase Ovid (1980 to 30 March 2017) (Appendix 3);
- LILACS (Latin American and Caribbean Health Science Information database (1982 to 30 March 2017) (Appendix 4);
- OpenGrey (System for Information on Grey Literature in Europe) (www.opengrey.eu/; searched 30 March 2017) (Appendix 5);
- ZETOC (1993 to 30 March 2017) (Appendix 6);
- ISRCTN registry (www.isrctn.com/editAdvancedSearch; searched 30 March 2017) (Appendix 7);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 30 March 2017) (Appendix 8);
- World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp; searched 30 March 2017) (Appendix 9).

Searching other resources

We made additional efforts to identify potential RCTs relevant to the topic from the references (and references of references) cited in primary sources. We did not impose any language restriction.

Data collection and analysis

Selection of studies

Two review authors (RM and OG) independently assessed the titles and abstracts of studies identified by relevance and design. We obtained full-text versions of the articles if they appeared to meet the inclusion criteria in the initial assessment of studies. A third review author (AW) evaluated any discrepant judgements.

Data extraction and management

Two review authors (MB and MQ) independently extracted data using a standardised data collection form that included information on the name of the first author, year of publication, study design, study population and study setting. In addition to information pertaining to participant characteristics, study inclusion and exclusion criteria, details of the interventions compared and study outcomes, we extracted information on study methodology. This included the method of randomisation, allocation concealment, frequency and handling of withdrawals, and adherence to the intention-to-treat principle. We resolved disagreements through discussion and in consultation with a third review author (AW) as required.

Assessment of risk of bias in included studies

Two review authors (MB and MQ) independently assessed and rated the methodological quality of each trial using the Cochrane tool for assessing risk of bias as in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We judged the quality of the studies by evaluating them for the following domains:

1. Random sequence generation.
2. Allocation concealment.
3. Masking of participants and personnel, and outcome assessment.
4. Incomplete outcome data.
5. Selective outcome reporting.
6. Funding source.
7. Other potential sources of bias.

We evaluated each study and assessed it separately for these domains. We judged each explicitly as follows:

- Low risk of bias.
- High risk of bias.
- Unclear risk (lack of information or uncertainty over the potential for bias).

We entered the data on what was reported to have happened in the study in the 'Risk of bias' table in Review Manager 5 (Review Manager 5 2014). We present summary figures of the 'risk of bias in included studies' in the review. These provides a context for discussing the reliability of the results of this review. We resolved any disagreement by referring to a third review author (AW) to reach a consensus.

Measures of treatment effect

We calculated summary estimates of treatment effect with 95% confidence intervals (CIs) for each comparison. Our measure of treatment effect was the risk ratio (RR) for dichotomous outcomes and the mean difference (MD) for continuous outcomes. Currently the review only includes analysis of dichotomous outcomes.

Unit of analysis issues

The unit of randomisation was the eye of individual trial participants. We did not anticipate that studies would have more than one eye affected in each individual; however, if this occurred we planned to note it in the review. If studies using a paired design were eligible for inclusion (i.e. studies assigning one eye to treatment and the fellow eye to control), we planned to use the generic inverse variance method to combine the results of such studies with those of studies randomising only one eye for each participant.

Dealing with missing data

No simple solution exists for the problem of missing data. We planned to handle this problem by contacting the investigators, whenever possible, to ensure that no data were missing for their study. We also planned to make explicit the assumptions of whatever method we used to cope with missing data.

Assessment of heterogeneity

We evaluated clinical heterogeneity (differences between studies in key characteristics of the participants, interventions or outcome measures). In the absence of clinical heterogeneity, we used the I^2 statistic to describe the percentage of total variation across studies that is due to heterogeneity rather than chance (Higgins 2003). An I^2 greater than 50% may represent substantial or considerable statistical heterogeneity (Higgins 2011). The importance we placed on the observed value of I^2 depended on (i) magnitude and direction of effects, and (ii) strength of evidence for heterogeneity (P value from the Chi^2 test and confidence interval for I^2).

We also used visual inspection of the graphic representation of studies with their 95% CIs to assess heterogeneity. We generated tables and graphs using the analysis module included in RevMan (Review Manager 5 2014). We represent pooled risk ratios pictorially as a 'forest plots' to permit visual examination of the degree of heterogeneity between studies.

Assessment of reporting biases

We assessed reporting bias through careful attention to quality assessment, particularly methodology. We planned to use funnel plot analysis to assess publication bias if there were more than 10 studies included in the meta-analysis. We also planned to use the Egger test (Egger 1997) to assess funnel plot asymmetry. A thorough search for unpublished studies through grey literature searches and contact with known experts in the field also helped to reduce the risk of publication bias.

Data synthesis

The results concentrate on the objectives and comparisons specified in the protocol for our review. We pooled data using a random-effects model, because it was likely that the effects of topical NSAIDs may vary between studies. The random-effects model takes into account between-study variability as well as within-study variability. When there were three or fewer trials, we used a fixed-effect model. We performed meta-analyses using RevMan 5 software (Review Manager 5 2014).

Subgroup analysis and investigation of heterogeneity

We planned to investigate heterogeneity by performing two subgroup analyses based on intuitive reasons. Firstly, we planned to perform subgroup analysis of different types of topical NSAIDs (for example, subgroup analysis of topical diclofenac and topical ketorolac). Secondly, we planned to perform subgroup analysis of traumatic corneal abrasions with different aetiologies, based on whether the abrasions are iatrogenic (arising from foreign body removal) or non-iatrogenic in origin.

Sensitivity analysis

Finally, we planned to perform sensitivity analyses to test how sensitive the results were to reasonable changes in the assumptions that we made and in the methods for combining the data (Lau 1998). We planned to perform sensitivity analysis for randomised versus quasi-randomised studies and eventually good-quality studies versus poor-quality studies.

Summary of findings

We used the principles of the GRADE system (Lau 1998) to assess the quality of the body of evidence associated with the primary outcome measure of this review (pain relief), and constructed a 'Summary of findings' (SoF) table using the GRADE software (GRADEpro 2014). The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence considers within-study risk of bias (methodological quality), the directness of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias.

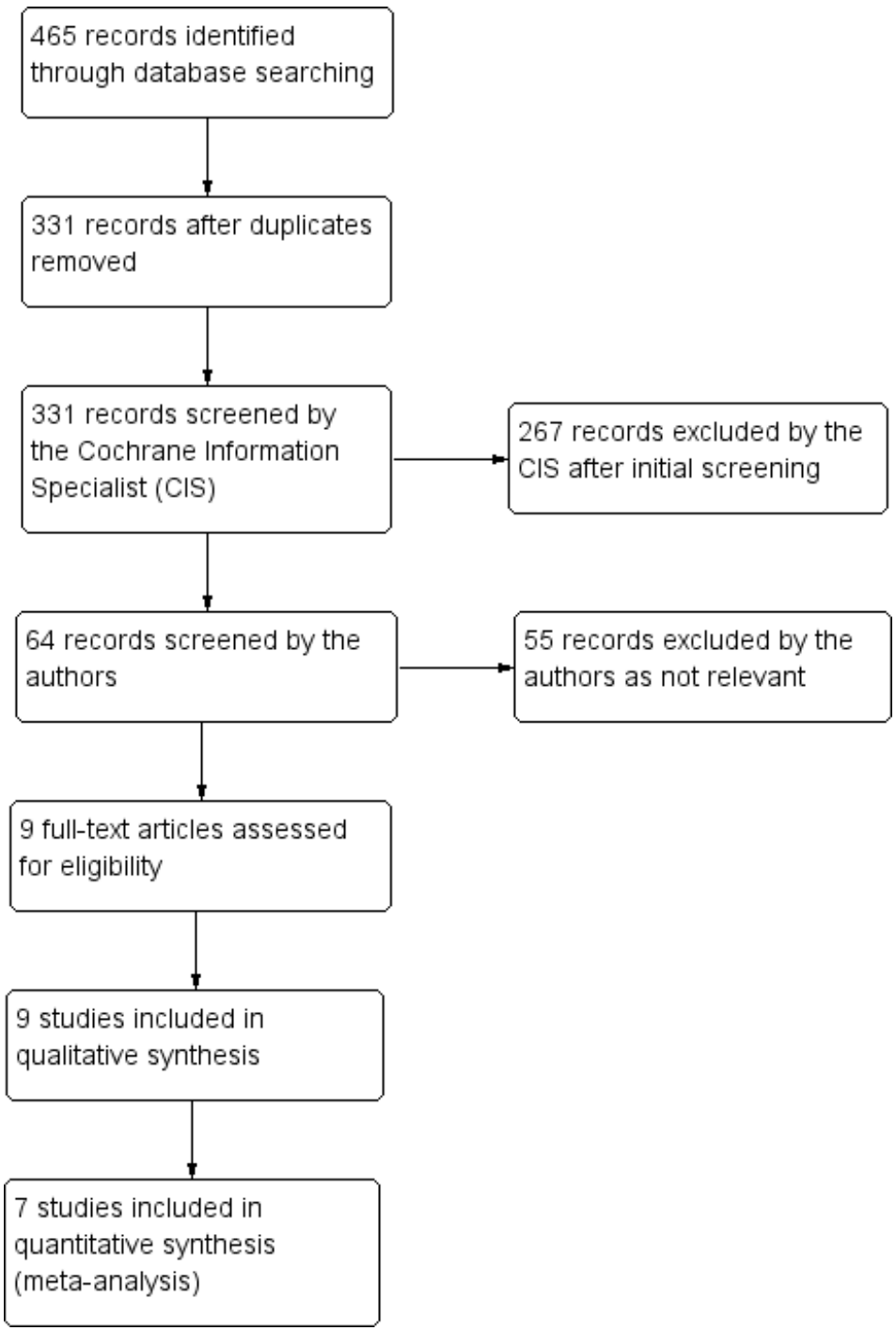
RESULTS

Description of studies

Results of the search

The electronic searches yielded 465 references (Figure 1). After 134 duplicate were removed the Cochrane Information Specialist (CIS) screened the remaining 331 records and removed 267 references which were not relevant to the scope of the review. We screened the remaining 64 references and obtained the full-text reports of nine references for further assessment. We assessed the nine full-text versions of the abstracts and all met the a priori criteria for inclusion in the final analysis. See Characteristics of included studies for details. We did not identify any ongoing studies from our searches of the clinical trials registries.

Figure 1. Study flow diagram.



Included studies

We included nine studies in this review (Alberti 2001; Brahma 1996; Donnenfeld 1995; Goyal 2001; Jayamanne 1997; Kaiser 1997; Patrone 1999; Solomon 2000; Szucs 2000). The interventions compared in this review were diverse (Table 1).

Excluded studies

We did not exclude any study after obtaining the full text of the report.

Risk of bias in included studies

We evaluated the overall quality of each study according to the methodology detailed in Assessment of risk of bias in included studies. The Characteristics of included studies table presents different 'Risk of bias' domains. Figure 2 and Figure 3 present a graph and summary of the risk of bias of included studies.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

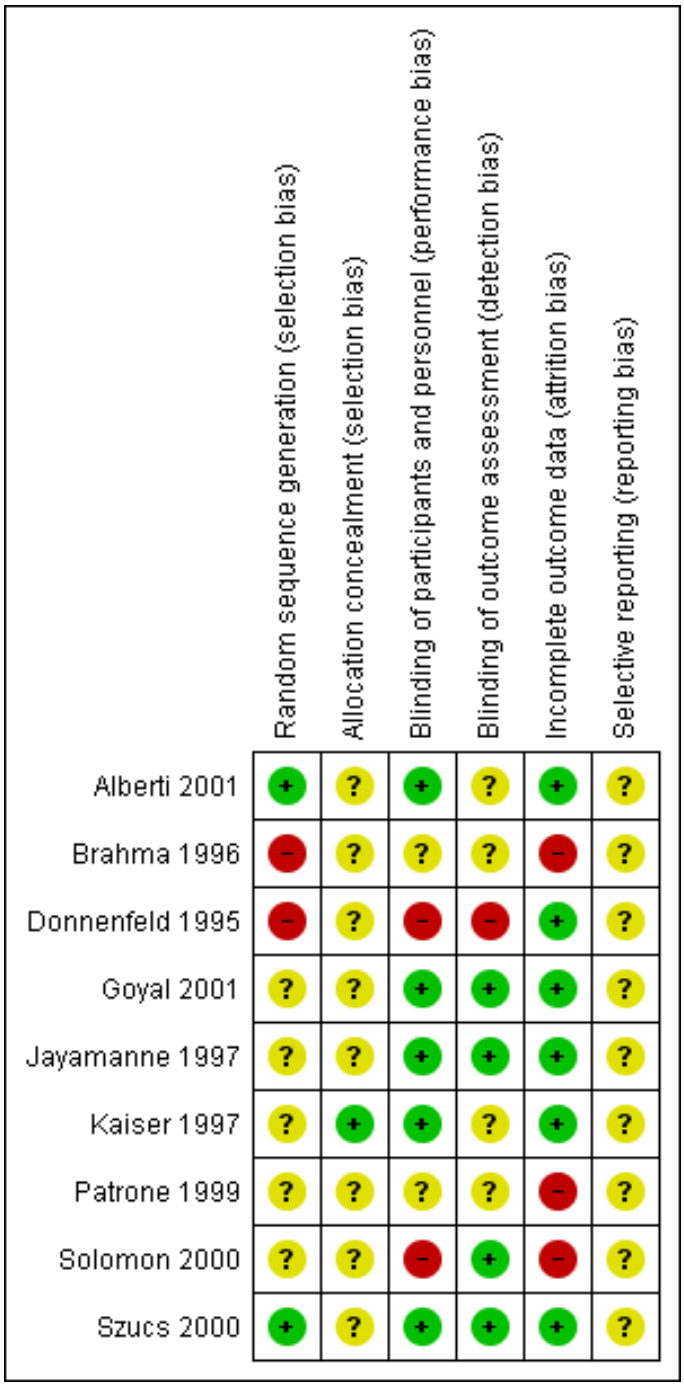
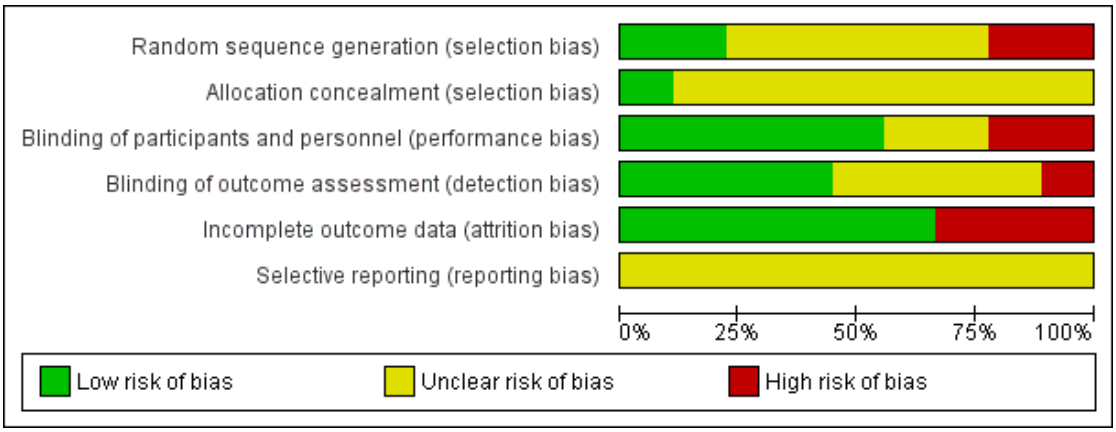


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Random sequence generation

Two of the studies (Brahma 1996; Donnenfeld 1995) were at a high risk of bias due to an inadequate method of sequence generation. We rated five of the studies at an unclear risk, since there was no explicit statement about the method for sequence generation.

Allocation concealment

Eight of the studies had an unclear risk of bias because there was no explicit statement about allocation concealment.

Blinding

Performance bias

In one study, the nature of the interventions was such that double-masking was not feasible (Solomon 2000). In two of the included studies, there was no explicit statement about masking of participants or study personnel (Brahma 1996; Patrone 1999).

Detection bias

There was a high risk of detection bias in one of the studies (Donnenfeld 1995). In four of the included studies there was a low risk of bias (Goyal 2001; Jayamanne 1997;Solomon 2000; Szucs 2000). The risk of detection bias was unclear in four studies because no explicit statement about masking of outcome assessors was reported (Alberti 2001; Brahma 1996; Kaiser 1997; Patrone 1999).

Incomplete outcome data

Three of the included studies had a high risk of attrition bias (Brahma 1996; Patrone 1999; Solomon 2000).

Selective reporting

We judged all studies to have an unclear risk, since no protocol or trial registry entry was available and it was therefore not possible to assess this domain.

Other potential sources of bias

We did not identify any other potential sources of bias.
Given the relatively small number of included trials, we were unable to assess publication bias (Higgins 2011).

Effects of interventions

See: **Summary of findings for the main comparison** Topical NSAIDs compared to control for analgesia in traumatic corneal abrasions

Primary outcome measures

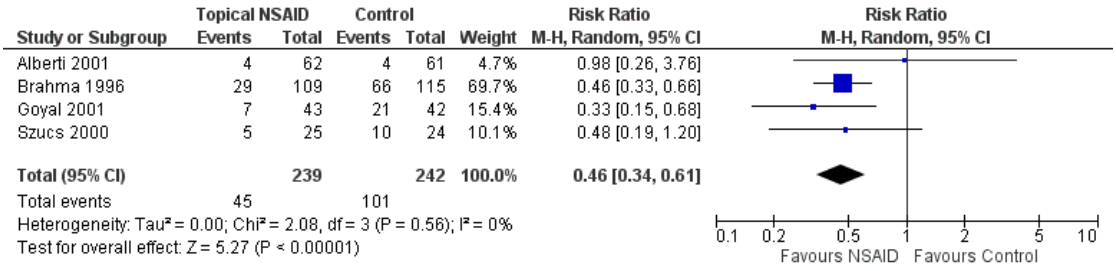
None of the included studies reported the primary outcome measures of this review (participant-reported pain intensity reduction of 30% or more at 24 hours and participant-reported pain intensity reduction of 50% or more at 24 hours).

Secondary outcome measures

Use of 'rescue' analgesia (that is, oral analgesia) at 24 hours, 48 hours and 72 hours

Four studies reported 'rescue' analgesia at 24 hours as an outcome measure (Alberti 2001; Brahma 1996; Goyal 2001;Szucs 2000) (participants reported = 481). Although these studies employed different comparators (Table 1), we pooled the data, since the treatment effect was in the same direction and the results were consistent. Participants taking NSAIDs were less likely to require rescue analgesia (low-certainty evidence); (risk ratio (RR) 0.46, 95% confidence interval (CI) 0.34 to 0.61; Analysis 1.1; Figure 4).

Figure 4. Forest plot of comparison: 1 Topical NSAIDs versus placebo/standard care, outcome: 1.1 Use of rescue oral analgesia at 24 hours.



None of the included studies reported 'rescue' analgesia at 48 hours or at 72 hours as an outcome measure.

Percentage/proportion healed after 24 and 48 hours (healing should have been ascertained using fluorescein staining or slit-lamp examination)

One study reported the proportion of corneal abrasions that were healed after 24 and 48 hours (Solomon 2000) (participants reported = 28). Ninety-three per cent of abrasions were healed within 24 hours and the remainder within 48 hours. There was no difference in the proportion of abrasions healed between groups (low-certainty evidence); 24 hours (RR 1.00, 95% CI 0.81 to 1.23); 48 hours (RR 1.00, 95% CI 0.88 to 1.14; Analysis 1.2 and Analysis 1.3).

Complications of corneal abrasion (as defined by the study authors)

Six of the studies reported complications of corneal abrasion as an outcome measure (Alberti 2001; Brahma 1996; Goyal 2001; Jayamanne 1997; Kaiser 1997; Szucs 2000) (participants reported = 609). Four of these studies (Brahma 1996; Goyal 2001; Jayamanne 1997; Szucs 2000) reported no complications in either study arm. One study (Alberti 2001) reported a corneal abscess in the comparator group and one study (Kaiser 1997) reported that three participants returned with a recurrent corneal erosion (two in the control group and one in the NSAID group) (very low-certainty evidence); (RR 0.44, 95% CI 0.07 to 2.96; Analysis 1.4).

Whether the use of concurrent topical antibiotics with additional lubricating effects reduced pain

None of the studies reported whether use of concurrent topical antibiotics (drops or ointments) with additional lubricating effects reduced pain.

Drug-related adverse events

Two studies reported on drug-related adverse events as an outcome measure (Alberti 2001; Jayamanne 1997) (participants reported = 163). Jayamanne 1997 reported no drug-related events, while Alberti 2001 reported four events (three in the NSAID group, including discomfort/photophobia on instillation, conjunctival hyperaemia and urticaria and one in the control group, corneal

abscess) very low-certainty evidence; (RR 2.95 95% CI 0.32 to 27.60; Analysis 1.5).

Other adverse events (as defined by the study authors)

None of the nine included studies reported other adverse events as an outcome measure.

DISCUSSION

Summary of main results

None of the included studies reported the primary outcome measures of this review, namely participant-reported pain intensity reduction of 30% or more or of 50% or more at 24 hours. A 30% reduction in pain intensity represents a clinically important difference in pain severity that corresponds to patients' perception of adequate pain control (Lee 2003; Younger 2009).

Four trials that randomised 664 participants (481 reported) to receive NSAIDs or placebo/standard care reported on the use of 'rescue' analgesia at 24 hours as a proxy measure of pain control. These trials were associated with a reduction in the need for oral analgesia (RR 0.46, 95% CI 0.34 to 0.61).

One trial, in which 28 participants were randomised, reported on the proportion of abrasions healed after 24 and 48 hours. These levels were similar between both arms of the trial.

Two trials (163 participants randomised) reported on drug-related adverse events, with rates low and similar between the intervention and control groups.

Overall completeness and applicability of evidence

The review has revealed a lack of high-quality evidence to support the use of topical NSAIDs in traumatic corneal abrasion.

Quality of the evidence

Despite seven of the nine included studies being conducted following the publication of the CONSORT statement in 1996, the trials were generally poorly reported. Allocation concealment was unclear and in the absence of a protocol or trial registration it was not possible to assess reporting bias. Several of the trials were associated with missing outcome data that were sufficient to have a clinically relevant impact on the effect estimate.

Potential biases in the review process

As far as we are aware, we have minimised potential biases in the review process. We followed all methods set out in the published protocol and all potentially eligible studies were included. Assessment or risk of bias was limited by poor reporting and the absence of published protocols or trial registration.

Agreements and disagreements with other studies or reviews

A previous systematic review of topical NSAIDs for corneal abrasions (Calder 2005) included 11 RCTs, of which three were included in a meta-analysis of self-reported pain scores at 24 hours. NSAIDs were found to reduce self-reported pain (weighted mean difference (WMD) -1.3 (95% CI -1.03 to 1.56)). The authors of this review concluded that topical NSAIDs can provide effective analgesia for people with traumatic corneal abrasions.

AUTHORS' CONCLUSIONS

Implications for practice

Traumatic corneal abrasions are a common presentation in both general emergency departments and specialist eye units. However, there remains a lack of high-quality evidence to inform the management of this condition. Prophylactic antibiotics with or without cycloplegia are typically used, although based on the results of a previous Cochrane Review (Lim 2016) eye patching is no longer recommended. Most simple traumatic abrasions heal within one or two days, but during this period they can be associated with significant pain, foreign body sensation and photophobia. It has been suggested that topical NSAIDs may be used to provide effective analgesia, which could potentially reduce the requirement for oral analgesia, although there have been some concerns in the literature regarding possible impairment of corneal wound healing and drug-induced adverse reactions.

The findings from the trials included in this review do not provide strong evidence to support the use of topical NSAIDs in traumatic corneal abrasions. This is important, since topical NSAIDs are associated with a higher cost compared to oral analgesics. None of the trials addressed our primary outcome measure of participant-reported pain intensity reduction of 30% or more or 50% or more at 24 hours.

Although there was some evidence from four trials that the use of topical NSAIDs led to a reduced need for 'rescue' analgesia at 24 hours, this finding should be interpreted with caution, since the certainty of the evidence was low.

Implications for research

Investigators planning future trials on the effectiveness of topical NSAIDs for corneal abrasions should attempt to address the sources of bias identified in the studies included in this review; specifically the use of appropriate methods for randomisation and allocation concealment. Furthermore, strategies should be developed to improve collection of outcome data and reduce attrition bias. Although the use of unidimensional visual analogue scales (VASs) has been shown to be a valid and reproducible method in studies evaluating pain relief, investigators may be tempted to overestimate the clinical importance of small differences in VAS scores. Further work in this context should attempt to determine the minimum clinically important difference as measured by VAS pain scores that represents small, moderate, or large treatment effects.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Alberti 2001

Methods	*Study design:* double-masked, randomised controlled trial Study centre: multicentre (6 sites) *Number randomised:* 126 *Losses to follow-up:* 3 *Number analysed:* 123 *Sample size calculation*: not reported
Participants	*Country:* France and Portugal *Age (SD):* 38.1 (15.9) *% Male:* 82.1% *Inclusion Criteria:* outpatients of either sex, aged over 18 years, with traumatic corneal abrasion or requiring ablation of a superficial corneal foreign body and/or curettage, and in whom the pain due to the lesion was > 20 mm on a horizontal VAS; 0 mm = no pain, 100 mm = unbearable pain *Exclusion criteria:* previous intolerance to the tested products or any NSAID or aminoglycoside, local or systemic anti-inflammatory treatment within the 5 days before the initial visit, systemic analgesia within the 24 hours before the initial visit, evolutive ocular pathology, any other concomitant traumatic lesion of the eye, deep corneal lesion, abrasions caused by contact lenses or chemical agents, plant foreign body still present on the cornea at the initial visit, complications of a traumatic corneal lesion requiring any treatment other than the study treatments, and monophthalmia
Interventions	*Intervention:* indomethacin 0.1%/gentamicin sulfate 300,000 IU/100 mL eye drops, 4 times daily for 4 - 5 days *Comparator:* gentamicin sulfate 300 mg/100 mL eye drops, 4 times daily for 4 - 5 days *Interventions received by both groups:* none *Other study arms not included in this review: n*one *Length of follow-up:* 4 - 5 days
Outcomes	*Primary outcome(s):* pain on a horizontal VAS *Secondary outcome(s):* evaluation of associated symptoms (photophobia, tearing, burning, irritation and foreign body sensation on a 0 - 3 scale (0 = absent; I = mild; 2 = moderate; 3 = severe); conjunctival hyperaemia and ciliary injection at day 0, day 1, and day 4/5 visits using the same 0 - 3 severity scale; surface area of the corneal abrasion at each visit; use of systemic analgesics *Adverse events reported (Y/N):* Y *Intervals at which outcome(s) assessed:* baseline (T0), one hour after first treatment instillation (T1), one hour after the second treatment instillation on day 0 (T2) and then on day 1 and day 4 or 5
Notes	*Study dates*: January to June 1998 *Trial registration:* not reported *Funding source(s):* Laboratoire Chauvin *Declaration of interest:* not reported

Alberti 2001 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation list was established using the PROC RANUNI procedure (SAS® Institute)." p235
Allocation concealment (selection bias)	Unclear risk	Comment: there is no explicit statement about the method used to conceal allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "This was a randomised, double-masked, parallel- group study carried out from January to June '98 at six centres, in France and Portugal." p234
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: there is no explicit statement about masking of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: > 80% follow-up. Reasons for missing data provided and any imbalance unrelated to the outcome
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol or trial registry entry available and therefore not possible to assess

Brahma 1996

Methods	*Study design:* randomised controlled trial *Study centre:* single centre *Number randomised:* 401 *Losses to follow-up:* 177 *Number analysed:* 224 *Sample size calculation*: stated that statistical advice was sought to determine sample size for a significance level of 5%
Participants	*Country:* UK *Age (SD):* 33.7 (SD not reported) *% Male:* 80.6% *Inclusion criteria:* participants with corneal abrasions and foreign bodies attending an emergency eye centre *Exclusion criteria:* participants < 16 years; pregnant women; those with a history of herpes simplex keratitis; known hypersensitivity to NSAIDs

Brahma 1996 (*Continued*)

Interventions	*Interventions:* flurbiprofen 0.03% eye drops 4 times daily for 48 hours; homatropine 2% eye drops at presentation only and flurbiprofen 0.03% eye drops 4 times daily for 48 hours *Comparators:* polyvinyl alcohol 1.4% (Liquifilm Tears) 4 times daily for 48 hours; homatropine 2% eye drops at presentation only *Interventions received by all groups:* chloramphenicol 1% eye ointment, 4 times daily for 5 days *Other study arms not included in this review:* none Length of follow-up: 24 hours
Outcomes	*Primary outcome(s):* ocular pain on a 10-cm linear VAS (where 0 = no pain and 10 = worst pain ever experienced) *Secondary outcome(s):* oral analgesia (Y/N); sleep disturbance (normal/disturbed); time off work due to eye injury *Adverse events reported (Y/N):* Y *Intervals at which outcome(s) assessed:* every 6 hours for 24 hours
Notes	*Study dates:* August 1993 - December 1993 *Trial registration:* not reported *Funding source(s):* Allergan UK provided study medications *Declaration of interest:* "None of the authors has any financial interest in Allergan Therapeutics"

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Patients were consecutively allocated at random to one of four treatment groups (table1)". p186
Allocation concealment (selection bias)	Unclear risk	Comment: there is no explicit statement about the method used to conceal allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: there is no explicit statement about masking of participants and study personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: there is no explicit statement about masking of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: high attrition (> 40%). Missing data likely to bias results
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol or trial registry entry available and therefore not possible to

Brahma 1996 (*Continued*)

		assess

Donnenfeld 1995

Methods	*Study design:* single-masked, randomised controlled trial *Study Centre:* multicentre (2 sites) Number randomised: Not reported *Losses to follow-up:* Not reported *Number analysed:* 47 *Sample size calculation*: not reported
Participants	*Country:* USA *Age (SD):* 34.9 (11.7) % Male: Not reported *Inclusion criteria:* traumatic corneal abrasion of < 24-hour duration *Exclusion criteria:* monocular vision; a history of wound healing problems (e.g. collagen vascular disease or corticosteroid use); usage of other ocular medications or oral NSAIDs; dry eyes; blepharitis; systemic infections; and contact lens-related epithelial defects
Interventions	*Intervention:* ketorolac tromethamine 0.5% eye drops, 4 times daily *Comparator:* placebo (Tears Plus), 4 times daily *Interventions received by both groups:* bandage contact lens, single instillation of cyclopentolate 1% eye drops, polymyxin B sulphate/trimethoprim hemisulfate eye drops 4 times daily *Other study arms not included in this review:* single instillation of polymyxin B sulphate/trimethoprim hemisulfate, single instillation of cyclopentolate 1% and a standard pressure patch *Length of follow-up:* 1 - 3 days (until resolution of corneal epithelial defect)
Outcomes	*Primary outcome(s):* time to resolution of corneal epithelial defect *Secondary outcome(s):* level of pain, photophobia, ocular irritation, redness, headache, tearing; ability to return to normal activities *Adverse events reported (Y/N):* Y *Intervals at which outcome(s) assessed:* psychometric testing at baseline and follow-up day 1, corneal epithelial defect monitored to resolution
Notes	*Study dates:* June 1993 - April 1994 *Trial registration:* not reported *Funding source(s):* Lions Club International; Allergan Pharmaceuticals *Declaration of interest:* not reported

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Quote: "Patients were assigned randomly to one of three treatment groups." p 980 Comment: there are no details on the

Donnenfeld 1995 (*Continued*)

		method of randomisation. Although participants were "randomly assigned" to 1 of 3 groups, from the results table, the randomisation seemed to be highly predictable, i.e. case numbers in each group were separated by 3
Allocation concealment (selection bias)	Unclear risk	Comment: there is no explicit statement about the method used to conceal allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "This was done in a single-masked randomised fashion. The patients in groups B and C were instructed to administer a drop of both the polymyxin B sulfate/ trimethoprim sulfate and the contents of the masked bottle four times daily, 5 minutes apart." p 980 Comment: study described as 'single masked' and study personnel were unmasked
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Forty-seven consecutive patients with traumatic corneal abrasions were randomised prospectively in a single-masked, controlled clinical trial ..." p 980 Comment: "Single-masked" was referring to the participant, therefore, assessors were not masked to the allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: data on all participants reported
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol or trial registry entry available and therefore not possible to assess

Goyal 2001

Methods	*Study design:* double-masked, randomised controlled trial *Study Centre:* single centre *Number randomised*: 88 *Losses to follow-up:* 3 *Number analysed:* 85 *Sample size calculation*: sample size calculated on basis of 80% power and significance level of 5%

Goyal 2001 (*Continued*)

Participants	*Country:* UK *Age (SD):* 39.5 (SD not reported) *% Male:* 77% *Inclusion criteria:* corneal abrasion within the last 48 hours; foreign body removal within the last 48 hours; age 16 - 80 yrs; no prior treatment *Exclusion criteria:* contact lens wear; signs of infiltration or infection; large erosion ⅓ of corneal surface; previous corneal surface disease (e.g. corneal dystrophies)
Interventions	*Intervention:* ketorolac trometamol 0.5% eye drops, 4 times daily *Comparator:* placebo (Liquifilm Tears), 4 times daily *Interventions received by both groups:* single instillation of cyclopentolate 0.5% eye drops; cyclopentolate 1% ointment *Other study arms not included in this review:* N/A *Length of follow-up:* followed up daily until complete healing had occurred
Outcomes	*Primary outcome(s):* improvement in pain, photophobia grittiness, wateriness and blurred vision (assessed using a VAS where 0 = no symptoms and 5 = worst symptoms) *Secondary outcome(s):* corneal epithelial healing; use of oral analgesics *Adverse events reported (Y/N):* Y *Intervals at which outcome(s) assessed:* psychometric testing at baseline and 24 hours
Notes	*Study dates:* not reported *Trial registration:* not reported *Funding source(s):* not reported *Declaration of interest:* not reported

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: no explicit statement about the method of randomisation
Allocation concealment (selection bias)	Unclear risk	Comment: there is no explicit statement about the method used to conceal allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Neither the examining doctor nor the patient was aware as to the nature of the drops." p 177
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Neither the examining doctor nor the patient was aware as to the nature of the drops." p 177
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Eighty-eight patients were enrolled in the study. Three were excluded as they either did not fulfil the eligibility cri-

Goyal 2001 (*Continued*)

		teria or had failed to attend for follow [up]. " p 177 Comment: > 95% of participants completed the study
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol or trial registry entry available and therefore not possible to assess

Jayamanne 1997

Methods	*Study design:* double-masked, randomised controlled trial *Study centre:* single centre *Number randomised*: 40 *Losses to follow-up:* 0 *Number analysed:* 40 *Sample size calculation*: not reported
Participants	*Country:* UK *Age (SD):* not reported *% Male:* not reported *Inclusion criteria:* participants aged > 18 years presenting within 24 hours of a unilateral corneal abrasion and no other injury *Exclusion criteria:* previous corneal pathology, including dystrophies and recurrent erosion syndrome, diabetes, those under 18 years of age or with known hypersensitivity to either NSAIDs or chloramphenicol
Interventions	*Intervention:* diclofenac 0.1% eye drop 4 times daily in the affected eye *Comparator:* normal saline eye drop 4 times daily in the affected eye *Interventions received by both groups:* chloramphenicol eye ointment *Other study arms not included in this review:* none *Length of follow-up:* until complete healing had occurred (all healed within 96 hours)
Outcomes	*Primary outcome(s):* pain measured with a VAS (a horizontal line measuring 10 cm in length showing a continuum from "no pain" to "worst pain ever"); categorical scale (none, mild discomfort not requiring painkillers, moderate pain requiring painkillers or severe disabling pain); and sub-categorisation into foreign body sensation, light sensitivity and headache-like deep pain within the eye and rating for the sub-categories as none, mild, moderate or severe *Secondary outcome(s):* none *Adverse events reported (Y/N):* Y *Intervals at which outcome(s) assessed*: baseline (day 0), day 1, day 2
Notes	*Study dates:* not reported *Trial registration:* not reported *Funding source(s):* not reported *Declaration of interest:* not reported

Jayamanne 1997 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to one of two treatment groups." p 79 Comment: there is no explicit statement about the method of randomisation
Allocation concealment (selection bias)	Unclear risk	Comment: there is no explicit statement about the method used to conceal allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The drops were dispensed in unmarked containers." p 79
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Doctors involved in the patient assessments were masked as to the study drug codes." p 80 Quote: "...no unmasking of patients occurred during the trial." p 80
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All patients completed the study as planned...". p 80
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol or trial registry entry available and therefore not possible to assess

Kaiser 1997

Methods	*Study design:* double-masked, randomised controlled trial. *Study centre:* single centre Number randomised: not reported (100 enrolled) *Losses to follow-up:* not reported (12 failed to complete due to ineligibility or loss to follow-up) *Number analysed:* 88 *Sample size calculation*: not reported
Participants	*Country:* USA *Age (SD):* 38.5 (9.0) *% Male:* 83% *Inclusion criteria:* aged > 18 years, with traumatic corneal abrasion or removal of superficial corneal foreign body of < 36 hours in duration; simple epithelial defect without stromal oedema, loss, or infiltrate; no prior treatment before being entered into the study; no other signs of ocular trauma; and no previous history of eye trauma or disease in the affected eye

Kaiser 1997 (*Continued*)

	Exclusion criteria: contact lens wear or had abrasions greater than 10 mm^2 in area
Interventions	*Intervention:* ketorolac tromethamine 0.5% ophthalmic solution 4 times daily *Comparator:* control vehicle drops 4 times daily Interventions received by both groups: cycloplegic drops (cyclopentolate 1% /phenylephrine 2.5%/tropicamide 0.25%) and erythromycin or polymyxin B (Polysporin) ophthalmic ointment *Other study arms not included in this review:* none *Length of follow-up:* not reported
Outcomes	*Primary outcome(s):* subjective symptoms: photophobia, tearing, foreign body sensation, and "blurry vision"; level of pain assessed on a scale of 0 - 10, with 0 representing no pain and 10 representing severe pain *Secondary outcome(s):* ability to return to normal activities *Adverse events reported (Y/N):* Y *Intervals at which outcome(s) assessed:* baseline (day 0), day 1, day 2
Notes	*Study dates:* not reported *Trial registration:* not reported *Funding source(s):* not reported *Declaration of interest:* not reported

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned in the eye emergency ward by the treating physician, who obtained an ocular medication bottle marked "A" or "B." p 1354 Comment: there is no explicit statement about the method of randomisation
Allocation concealment (selection bias)	Low risk	Quote: "The contents of bottle "A" or "B" were known only by the two authors, who did not enrol patients in the study." p 1354
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both the physician and the patient were unaware of which bottle contained the ketorolac tromethamine 0.5% ophthalmic solution." p 1354
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: there is no explicit statement about masking of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: low attrition and missing data balanced across arms

Kaiser 1997 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Comment: no protocol or trial registry entry available and therefore not possible to assess

Patrone 1999

Methods	*Study design:* randomised controlled trial *Study centre:* single centre *Number randomised:* 409 *Losses to follow-up:* 62 *Number analysed:* 347 *Sample size calculation*:not reported
Participants	*Country*: Italy *Age (SD):* 43.4 (15.7) *% Male:* 66.5% *Inclusion criteria:* corneal abrasion < 16 mm^2; no limbus and/or ocular structure involvement; occurred less than 12 hours before the clinical examination; no chronic ocular pathology or systemic pathologies or neurological/corneal pathologies able to influence corneal sensitivity; absence of corneal sensitivity impairments to the contralateral undamaged eye *Exclusion criteria:* participants with abrasions caused by thermal, radiant or caustic agents; contact lens-wearing participants; and one-eyed or functionally one-eyed participants
Interventions	*Intervention:* indomethacin 0.1% eye drops; netilmicin 0.3% every 4 hours *Comparator:* 0.3% netilmicin only every 4 hours *Interventions received by both groups:* bandage contact lens for 24 hours *Other study arms not included in this review:* N/A *Length of follow-up:* not recorded (monitored daily until healing of corneal abrasion)
Outcomes	*Primary outcome(s):* Subjective pain was evaluated using a VPS *Secondary outcome(s):* none *Adverse events reported (Y/N):* N *Intervals at which outcome(s) assessed:* 30 mins after the first medication (T0); during the first check-up (after 12 hours; T1), and during the second check-up (after 24 hours; T2)
Notes	*Study dates:* January 1994 - February 1997 *Trial registration:* not reported *Funding source(s):* not reported *Declaration of interest:* "The authors have no proprietary or financial interest in the development or marketing of this or any competing drug."

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**

Patrone 1999 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "The protocol randomised the patients into two homogeneous groups." p 351 Comment: there is no explicit statement about the method used for randomisation
Allocation concealment (selection bias)	Unclear risk	Comment: there is no explicit description about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: there is no explicit statement about masking of study participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: there is no explicit statement about masking of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Of the 409 patients who joined the study, 62 were excluded because they failed to respect the instructions of the protocol. " p 352 Comment: there were no data on the outcomes of the 62 excluded participants or reasons for dropout
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol or trial registry entry available and therefore not possible to assess

Solomon 2000

Methods	*Study design:* randomised controlled trial *Study centre:* single centre *Number randomised:* 28 *Losses to follow-up:* 0 *Number analysed:* 28 *Sample size calculation*: not reported
Participants	*Country:* Israel *Age (SD):* 32 (SD not reported) *% Male:* not reported *Inclusion criteria:* corneal epithelial abrasion (3 mm or less) following minor corneal trauma *Exclusion criteria:* not reported
Interventions	*Intervention:* indomethacin 1%, 4 times daily *Comparator:* semi-pressure patch *Interventions received by both groups:* single instillation of topical cyclopentolate 1% and

Solomon 2000 (*Continued*)

	chloramphenicol 0.3%, 3 times daily *Other study arms not included in this review:* none *Length of follow-up:* 24 hours
Outcomes	*Primary outcome(s):* pain, graded on a scale of 0 - 10; other symptoms including tearing, itching, burning, discharge, foreign body sensation, and photophobia graded on a scale from 0 - 3 *Secondary outcome(s):* objective signs including swelling or hyperaemia of the eyelid and conjunctival hyperaemia evaluated on a scale of 0 - 3; healing of corneal abrasion *Adverse events reported (Y/N):* N *Intervals at which outcome(s) assessed*: 6 - 9 hours after start of treatment follow-up 18 - 24 hours after the first visit
Notes	*Study dates:* not reported *Trial registration:* not reported *Funding source(s):* not reported *Declaration of interest*: not reported

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned into 1 of 2 treatment protocols." p 317 Comment: there is no explicit statement about the method of randomisation
Allocation concealment (selection bias)	Unclear risk	Comment: there is no explicit statement about the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: the nature of the comparator interventions were such that masking was not feasible
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The first eye examination was always performed by 1 of the authors (M.H.), whereas the follow-up examination was done by another author (J.F.-P.), who was unaware of the treatment used." p 317
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "After 6 to 9 hours, we recorded symptoms in 10 of the 14 patients in group 1 and 11 of the 14 patients in group 2; the other patients were not available." p 317 Comment: > 20% attrition for assessment at 9 hours, which may have biased results
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol or trial registry entry and therefore not possible to assess

Szucs 2000

Methods	*Study design:* double-masked, randomised controlled trial *Study centre:* single centre *Number randomised:* 49 *Losses to follow-up:* 0 *Number analysed:* 49 *Sample size calculation*: stated that sample size calculation was performed to determine the number of participants for a specified outcome
Participants	*Country:* USA *Age (SD):* 39.5 (SD not reported) *% Male:* 73% *Inclusion criteria:* aged 18 years or older with a traumatic corneal abrasion *Exclusion criteria:* history of recent eye surgery, glaucoma, ocular infection, other signs of ocular trauma; adverse reactions to diclofenac or NSAIDs including aspirin; any narcotic use within 6 hours of ED treatment; unavailable for telephone follow-up at 2 hours; minimal pain defined as a score of 3 or less on the NPIS; pregnancy, women of childbearing age in whom pregnancy could not be excluded by history of last menstrual period, and lactating women
Interventions	*Intervention:* single instillation of diclofenac 0.1% eye drops in the ED and then every 6 hours for 24 - 36 hours *Comparator:* control vehicle (Natural Tears) Interventions received by both groups: single instillation of cyclopentolate 0.5% eye drops, at the discretion of the treating physician; gentamicin 0.3% eye drops, every 2 hours for 24 hours *Other study arms not included in this review:* N/A Length of follow-up: 24 hours
Outcomes	*Primary outcome(s):* improvement of pain 2 hours after treatment *Secondary outcome(s):* need for rescue oral analgesia Adverse events reported (Y/N): Y *Intervals at which outcome(s) assessed:* 2 hours after start of treatment
Notes	*Study dates:* not reported *Trial registration:* not reported *Funding source(s):* not reported *Declaration of interest:* not reported

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients who had corneal abrasions detected by fluorescein uptake during slit lamp examination who signed consent were then randomly assigned by our institution's Pharmacy Investigational and Clinical Services using a Ciba-Geigy Scientific Random Number Table to re-

Szucs 2000 (*Continued*)

		ceive either diclofenac or control vehicle drops." p 132
Allocation concealment (selection bias)	Unclear risk	Comment: there is no explicit statement about the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Blinding was maintained with the use of identically labelled and masked bottles. The contents of the bottles were not visible through the masking." p 132 - 33
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The patient, physician, and nurse remained blinded to the medication throughout the entire study." p 133
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "We did not have complete follow-up for 1 patient who was reexamined by an ophthalmologist. This patient was ultimately excluded from the study. Pain scores at 2 hours were obtained for all patients enrolled in the study." p133
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol or trial registry entry and therefore not possible to assess

ED: emergency department
NPIS: numerical pain intensity score
IU: international units
NSAID: non-steroidal anti-inflammatory drug
RCT: randomised controlled trial
VAS: visual analogue scale
VPS: verbal pain scale

DATA AND ANALYSES

Comparison 1. Topical NSAIDs versus Control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Use of rescue oral analgesia at 24 hours	4	481	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.34, 0.61]
2 Proportion of abrasions healed after 24 hours	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Proportion of abrasions healed after 48 hours	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Complications of corneal abrasion	6	609	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.07, 2.96]
5 Drug-related adverse events	2	163	Risk Ratio (M-H, Fixed, 95% CI)	2.95 [0.32, 27.60]

Analysis 1.1. Comparison 1 Topical NSAIDs versus Control, Outcome 1 Use of rescue oral analgesia at 24 hours.

Review: Topical non-steroidal anti-inflammatory drugs for analgesia in traumatic corneal abrasions

Comparison: 1 Topical NSAIDs versus Control

Outcome: 1 Use of rescue oral analgesia at 24 hours

Study or subgroup	Topical NSAID n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Alberti 2001	4/62	4/61		4.7 %	0.98 [0.26, 3.76]
Brahma 1996	29/109	66/115		69.7 %	0.46 [0.33, 0.66]
Goyal 2001	7/43	21/42		15.4 %	0.33 [0.15, 0.68]
Szucs 2000	5/25	10/24		10.1 %	0.48 [0.19, 1.20]
Total (95% CI)	**239**	**242**		**100.0 %**	**0.46 [0.34, 0.61]**

Total events: 45 (Topical NSAID), 101 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.08$, df = 3 (P = 0.56); $I^2 = 0.0\%$

Test for overall effect: Z = 5.27 (P < 0.00001)

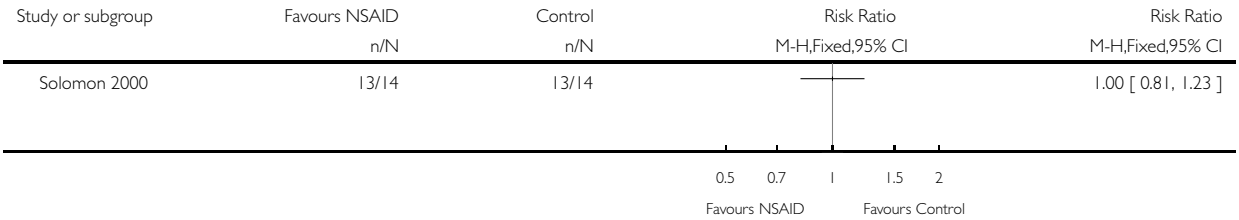
Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Topical NSAIDs versus Control, Outcome 2 Proportion of abrasions healed after 24 hours.

Review: Topical non-steroidal anti-inflammatory drugs for analgesia in traumatic corneal abrasions

Comparison: 1 Topical NSAIDs versus Control

Outcome: 2 Proportion of abrasions healed after 24 hours

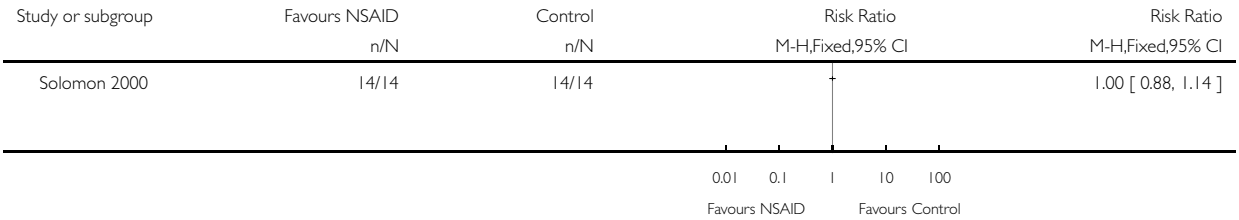


Analysis 1.3. Comparison 1 Topical NSAIDs versus Control, Outcome 3 Proportion of abrasions healed after 48 hours.

Review: Topical non-steroidal anti-inflammatory drugs for analgesia in traumatic corneal abrasions

Comparison: 1 Topical NSAIDs versus Control

Outcome: 3 Proportion of abrasions healed after 48 hours



Analysis 1.4. Comparison 1 Topical NSAIDs versus Control, Outcome 4 Complications of corneal abrasion.

Review: Topical non-steroidal anti-inflammatory drugs for analgesia in traumatic corneal abrasions

Comparison: 1 Topical NSAIDs versus Control

Outcome: 4 Complications of corneal abrasion

Study or subgroup	Topical NSAID n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Alberti 2001	0/62	1/61		35.6 %	0.33 [0.01, 7.90]
Brahma 1996	0/109	0/115			Not estimable
Goyal 2001	0/43	0/42			Not estimable
Jayamanne 1997	0/20	0/20			Not estimable
Kaiser 1997	1/43	2/45		64.4 %	0.52 [0.05, 5.56]
Szucs 2000	0/25	0/24			Not estimable
Total (95% CI)	**302**	**307**		**100.0 %**	**0.44 [0.07, 2.96]**

Total events: 1 (Topical NSAID), 3 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.05$, df = 1 (P = 0.82); $I^2 = 0.0\%$

Test for overall effect: Z = 0.84 (P = 0.40)

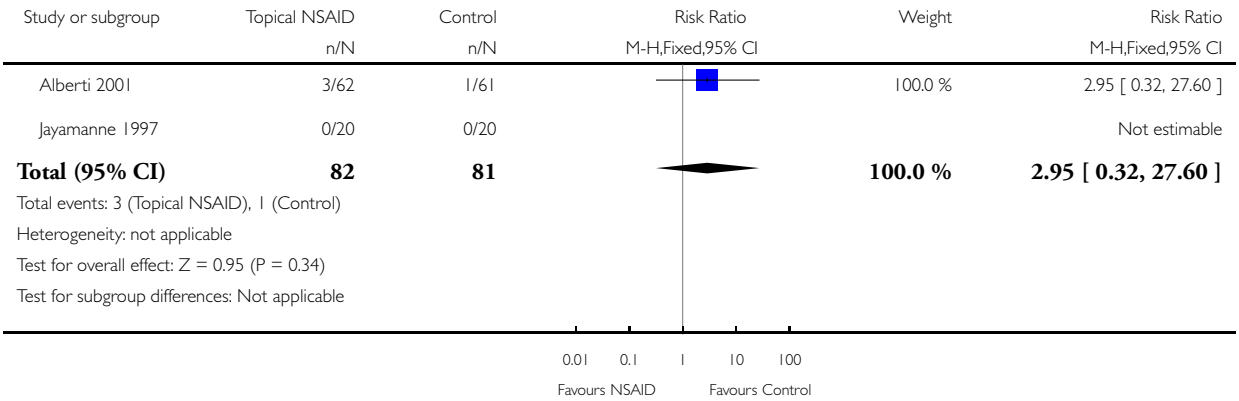
Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Topical NSAIDs versus Control, Outcome 5 Drug-related adverse events.

Review: Topical non-steroidal anti-inflammatory drugs for analgesia in traumatic corneal abrasions

Comparison: 1 Topical NSAIDs versus Control

Outcome: 5 Drug-related adverse events



ADDITIONAL TABLES

Table 1. Comparator interventions of included studies

Study	Intervention 1	Intervention 2	Comparator 1	Comparator 2
Alberti 2001	Topical NSAID (indomethacin 0.1%) + topical antibiotic	None	Topical antibiotic	None
Brahma 1996	Topical NSAID (flurbiprofen 0.03%) + topical antibiotic	Topical NSAID + cycloplegic + topical antibiotic	Placebo + topical antibiotic	Cycloplegic + topical antibiotic
Donnenfeld 1995	Topical NSAID (ketorolac 0.5%) + cycloplegic + topical antibiotic + bandage CL	None	Cycloplegic + topical antibiotic + bandage CL	Cycloplegic + topical antibiotic + pressure patch
Goyal 2001	Topical NSAID (ketorolac 0.5%) + cycloplegic + topical antibiotic	None	Placebo + cycloplegic + topical antibiotic	None
Jayamanne 1997	Topical NSAID (diclofenac 0.	None		

Table 1. Comparator interventions of included studies (*Continued*)

	1%) + topical antibiotic			
Kaiser 1997	Topical NSAID (ketorolac 0,1%) + cycloplegic + topical antibiotic	None	Placebo + cycloplegic + topical antibiotic	None
Patrone 1999	Topical NSAID (indomethacin 0.1%) + topical antibiotic + bandage CL	None	Topical antibiotic + bandage CL	None
Solomon 2000	Topical NSAID indomethacin 1%) + cycloplegic + topical antibiotic	None	Cycloplegic + topical antibiotic + pressure patch	None
Szucs 2000	Topical NSAID (diclofenac 0.1%) + cycloplegic + topical antibiotic	None	Placebo+ cycloplegic + topical antibiotic	None

CL: contact lens
NSAID: non-steroidal anti-inflammatory drug

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Cornea
#2 MeSH descriptor Corneal Diseases
#3 MeSH descriptor Eye Injuries
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Wounds and Injuries
#6 injur* or abrasion* or erosion* or trauma* or wound* or foreign bod*
#7 (#5 OR #6)
#8 eye* or cornea*
#9 (#7 AND #8)
#10 (#4 OR #9)
#11 MeSH descriptor Anti-Inflammatory Agents, Non-Steroidal
#12 nsaid*
#13 nonsteroidal anti-inflammator*
#14 non-steroidal anti-inflammator*
#15 MeSH descriptor Diclofenac
#16 diclofenac*
#17 fenoprofen*
#18 flurbiprofen*

#19 MeSH descriptor Indomethacin
#20 indometacin*
#21 MeSH descriptor Ketoprofen
#22 ketoprofen*
#23 ketorolac*
#24 piroxicam*
#25 bromfenac*
#26 nepafenac*
#27 oxyphenbutazone*
#28 suprofen*
#29 (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28)
#30 MeSH descriptor Analgesia
#31 analgesi*
#32 MeSH descriptor Pain
#33 pain*
#34 (#30 OR #31 OR #32 OR #33)
#35 (#10 AND #29 AND #34)

Appendix 2. MEDLINE OVID search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp cornea/
14. exp corneal diseases/
15. exp eye injuries/
16. or/13-15
17. exp "wounds and injuries"/
18. (injur$ or abrasion$ or erosion$ or trauma$ or wound$ or foreign bod$).tw.
19. or/17-18
20. (eye$ or cornea$).tw.
21. 19 and 20
22. 16 or 21
23. exp anti inflammatory agents non steroidal/
24. nsaid$.tw.
25. nonsteroidal anti-inflammator$.tw.
26. non-steroidal anti-inflammator$.tw.
27. exp diclofenac/
28. diclofenac$.tw.
29. fenoprofen$.tw.
30. flurbiprofen$.tw.
31. exp indometacin/

32. indometacin$.tw.
33. exp ketoprofen/
34. ketoprofen$.tw.
35. ketorolac$.tw.
36. piroxicam$.tw.
37. bromfenac$.tw.
38. nepafenac$.tw.
39. oxyphenbutazone$.tw.
40. suprofen$.tw.
41. or/23-40
42. exp analgesia/
43. analgesi$.tw.
44. Pain/
45. pain$.tw.
46. or/42-45
47. 22 and 41 and 46
48. 12 and 47

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

Appendix 3. Embase OVID search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)

32. 11 or 24 or 31
33. exp cornea/
34. exp cornea disease/
35. exp cornea epithelium/
36. exp eye injury/
37. or/33-36
38. exp injury/
39. (injur$ or abrasion$ or erosion$ or trauma$ or wound$ or foreign bod$).tw.
40. or/38-39
41. (eye$ or cornea$).tw.
42. 40 and 41
43. 37 or 42
44. exp nonsteroidal antiinflammatory agent/
45. nsaid$.tw.
46. nonsteroidal anti-inflammator$.tw.
47. non-steroidal anti-inflammator$.tw.
48. exp diclofenac/
49. diclofenac$.tw.
50. fenoprofen$.tw.
51. flurbiprofen$.tw.
52. exp indometacin/
53. indometacin$.tw.
54. exp ketoprofen/
55. ketoprofen$.tw.
56. ketorolac$.tw.
57. exp piroxicam/
58. piroxicam$.tw.
59. bromfenac$.tw.
60. nepafenac$.tw.
61. oxyphenbutazone$.tw.
62. suprofen$.tw.
63. or/44-62
64. exp analgesia/
65. analgesi$.tw.
66. eye pain/
67. pain$.tw.
68. or/64-67
69. 43 and 63 and 68
70. 32 and 69

Appendix 4. LILACS search strategy

injur$ or abrasion or erosion or trauma or foreign bod$ and eye$ or cornea$ and nonsteroidal antiinflammator$ or nonsteroidal anti inflammator$ or non steroidal anti inflammator$ or NSAID$ or diclofenac or fenoprofen or flurbiprofen or indometacin or ketoprofen or ketorolac or piroxicam or bromfenac or nepafenac or oxyphenbutazone or suprofen and analgesi$ or pain$

Appendix 5. OpenGrey search strategy

corneal abrasion and pain

Appendix 6. Zetoc search strategy

corneal abrasion and pain

Appendix 7. ISRCTN search strategy

corneal abrasion and pain

Appendix 8. ClinicalTrials.gov search strategy

Corneal Abrasion AND Pain

Appendix 9. WHO ICTRP search strategy

Corneal Abrasion AND Pain

Appendix 10. Risk of bias assessment

Risk of bias assessment (RoB assessment)			**Risk of bias ass**
Entry	**Judgement**	**Support for judgement**	
1. Random sequence generation (selection bias)	Low risk/High risk/Unclear risk	Quote:	
2. Allocation concealment (selection bias)	Low risk/High risk/Unclear risk	Quote:	
3. Masking of participants and personnel (performance bias)	Low risk/High risk/Unclear risk	Quote:	
4. Masking of outcome assessment (detection bias)	Low risk/High risk/Unclear risk	Quote:	
5. Incomplete outcome data	Low risk/High risk/Unclear risk	Quote:	
Date:_/_/_	Reviewer's signature:		

CONTRIBUTIONS OF AUTHORS

Abel Wakai (AW) wrote the drafts for the protocol/review and performed the GRADE assessment.

John Lawrenson (JL), Annali Lawrenson (AL), Ahmed Amayem (AA), Eddy Lang (EL) and Cathal Walsh (CW) reviewed and commented on the drafts.

Ryan McCormick (RM) and Omar Ghandour (OG) independently assessed the titles and abstracts of studies identified for relevance and design.

Michael Brown (MB) and Michael Quirke (MQ) independently abstracted data from the included studies and independently assessed and rated the methodological quality of each included study using the Cochrane tool for assessing risk of bias.

Yongjun Wang (YW) performed the GRADE assessment.

AW and JL responded to peer review comments.

DECLARATIONS OF INTEREST

Abel Wakai: none known

John Lawrenson: none known

Annali Lawrenson: none known

Yongjun Wang: none known

Michael Brown: none known

Michael Quirke: none known

Omar Ghandour: none known

Ryan McCormick: none known

Cathal Walsh: none known

Ahmed Amayem: none known

Eddy Lang: none known

Nick Harrison: none known

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol we stated that we would make additional efforts to identify potential RCTs relevant to the topic from the following data sources: references (and references of references) cited in primary sources; other unpublished sources known to experts in the specialty, raw data from published trials; contacting pharmaceutical companies. In this review, due to the comprehensive nature of our electronic searches, we did not seek information regarding potential RCTs relevant to the topic from known experts in the specialty or from pharmaceutical companies, and we did not seek raw data from the published trials.

We stated in the protocol that dichotomous outcomes would be described using relative (risk ratio) and absolute (risk difference) measures. In this review we only calculated risk ratios. Measures of absolute risk are included in the summary of findings table.