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Prophylactic non-steroidal anti-inflammatory drugs for the prevention of macular oedema after cataract surgery (Review)

Lim BX, Lim CHL, Lim DK, Evans JR, Bunce C, Wormald R

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[Intervention Review]

Prophylactic non-steroidal anti-inflammatory drugs for the prevention of macular oedema after cataract surgery

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ABSTRACT

Background

Macular oedema (MO) is the accumulation of extracellular fluid in the central retina (the macula). It may occur after cataract surgery and may give rise to poor visual outcome, with reduced visual acuity and distortion of the central vision. MO is often self-limiting with spontaneous resolution, but a small proportion of people with chronic persistent MO may be difficult to treat. Chronic oedema may lead to the formation of cystic spaces in the retina termed 'cystoid macular oedema' (CMO). Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in cataract surgery and may reduce the chances of developing MO.

Objectives

The aim of this review is to answer the question: is there evidence to support the prophylactic use of topical NSAIDs either in addition to, or instead of, topical steroids postoperatively to reduce the incidence of macular oedema (MO) and associated visual morbidity.

Search methods

We searched a number of electronic databases including CENTRAL, MEDLINE and Embase. Date last searched 2 September 2016.

Selection criteria

We included randomised controlled trials (RCTs) in which adult participants had undergone surgery for age-related cataract. We included participants irrespective of their baseline risk of MO, in particular we included people with diabetes and uveitis. We included trials of preoperative and/or postoperative topical NSAIDs in conjunction with postoperative topical steroids. The comparator was postoperative topical steroids alone. A secondary comparison was preoperative and/or postoperative topical NSAIDs alone versus postoperative topical steroids alone.

Data collection and analysis

Two review authors independently selected studies for inclusion, assessed risk of bias and extracted data using standard methods expected by Cochrane. We pooled data using a random-effects model. We graded the certainty of the evidence using GRADE and considered the following: risk of bias of included studies, precision of the effect estimate, consistency of effects between studies, directness of the outcome measure and publication bias.

Main results

We identified 34 studies that were conducted in the Americas, Europe, the Eastern Mediterranean region and South-East Asia. Over 5000 people were randomised in these trials. The majority of studies enrolled one eye per participant; a small subset (4 trials) enrolled a proportion of people with bilateral surgery. Twenty-eight studies compared NSAIDs plus steroids with steroids alone. Six studies compared NSAIDs with steroids. A variety of NSAIDs were used, including ketorolac, diclofenac, nepafenac, indomethacin, bromfenac, flurbiprofen and pranopfen. Follow-up ranged from one to 12 months. In general, the studies were poorly reported. We did not judge any of the studies at low risk of bias in all domains. Six studies were funded by industry, seven studies were funded from non-industry sources, and the rest of the studies did not report the source of funding.

There was low-certainty evidence that people receiving topical NSAIDs in combination with steroids may have a lower risk of poor vision due to MO at three months after cataract surgery compared with people receiving steroids alone (risk ratio (RR) 0.41, 95% confidence interval (CI) 0.23 to 0.76; eyes = 1360; studies = 5; I^2 = 5%). We judged this to be low-certainty evidence because of risk of bias in the included studies and indirectness, as the extent of visual loss was not always clear. Only one study reported poor vision due to MO at 12 months and we judged this to be very low-certainty evidence as there were only two events. Quality of life was only reported in one of the 34 studies comparing NSAIDs plus steroids versus steroids alone, and it was not fully reported, other than to comment on lack of differences between groups. There was evidence of a reduced risk of MO with NSAIDs at three months after surgery, but we judged this to be low-certainty due to risk of bias and publication bias (RR 0.40, 95% CI 0.32 to 0.49; eyes = 3638; studies = 21). There was inconsistent evidence on central retinal thickness at three months (I^2 = 87%). Results ranged from -30.9 µm in favour of NSAIDs plus steroids to 7.44 µm in favour of steroids alone. Similarly, data on best corrected visual acuity (BCVA) were inconsistent, but nine out of 10 trials reporting this outcome found between-group differences in visual acuity of less than 0.1 logMAR.

None of the six studies comparing NSAIDs alone with steroids reported on poor vision due to MO at three or 12 months. There was low-certainty evidence that central retinal thickness was lower in the NSAIDs group at three months (mean difference (MD) -22.64 µm, 95% CI -38.86 to -6.43; eyes = 121; studies = 2). Five studies reported on MO and showed a reduced risk with NSAIDs, but we judged this evidence to be of low-certainty (RR 0.27, 95% CI 0.18 to 0.41; eyes = 520). Three studies reported BCVA at three months and the results of these trials were inconsistent, but all three studies found differences of less than 0.1 logMAR between groups.

We did not note any major adverse events - the main consistent observation was burning or stinging sensation with the use of NSAIDs.

Authors' conclusions

Using topical NSAIDs may reduce the risk of developing macular oedema after cataract surgery, although it is possible that current estimates as to the size of this reduction are exaggerated. It is unclear the extent to which this reduction has an impact on the visual function and quality of life of patients. There is little evidence to suggest any important effect on vision after surgery. The value of adding topical NSAIDs to steroids, or using them as an alternative to topical steroids, with a view to reducing the risk of poor visual outcome after cataract surgery is therefore uncertain. Future trials should address the remaining clinical uncertainty of whether prophylactic topical NSAIDs are of benefit, particularly with respect to longer-term follow-up (at least to 12 months), and should be large enough to detect reduction in the risk of the outcome of most interest to patients, which is chronic macular oedema leading to visual loss.

PLAIN LANGUAGE SUMMARY

Prophylactic non-steroidal anti-inflammatory drugs (NSAIDs) for the prevention of macular oedema after cataract surgery

What is the aim of this review?

The aim of this Cochrane Review was to find out if NSAID eye drops can prevent a sight-threatening complication of cataract surgery (swelling at the back of the eye, known as macular oedema). Cochrane researchers collected and analysed all relevant studies to answer this question and found 34 studies.

Key messages

There is only low-certainty evidence to support the use of NSAID eye drops to prevent macular oedema affecting vision after cataract surgery.

What was studied in the review?

There is a clear lens in the eye that focuses the light on the back of the eye. As people get older this lens can become cloudy. A cloudy lens is known as a cataract. Doctors can remove the cataract and replace it with an artificial lens. This is usually a very successful operation. Occasionally, people having cataract surgery can get swelling at the back of the eye after the operation. This swelling is known as macular oedema. It usually gets better on its own accord, but if it persists it can result in poor vision.

NSAIDs are a medication that can treat inflammation. They may be able to reduce the chances of this swelling happening. The NSAIDs studied in this review were eye drops.

What are the main results of the review?

The review authors found 34 relevant studies. These studies were conducted in all parts of the world including the Americas, Europe, the Eastern Mediterranean region and South-East Asia. Most (28) of these studies compared NSAIDs combined with steroids against steroids alone. Some of the studies (6) compared NSAIDs with steroids alone. A variety of NSAIDs were used, including ketorolac, diclofenac, nepafenac, indomethacin, bromfenac, pranopfen and flurbiprofen. People taking part in these trials were followed up from between one and 12 months. Most studies only followed up to two months or less. Six studies were funded by industry; seven studies were funded from non-industry sources and the rest of the studies did not report the source of funding.

There was low-certainty evidence that NSAIDs reduce the chance of poor vision due to macular oedema three months after cataract surgery. Only one study reported on poor vision due to macular oedema at 12 months and we judged this to have very low-certainty of evidence.

Using NSAIDs was associated with a reduced risk of macular oedema but the review authors judged this to be low-certainty.

Inconsistent results were seen for some measurements of macular oedema, such as the thickness of the tissue at the back of the eye (central retinal thickness) at three months after surgery. This measurement was not reported by any studies at 12 months after surgery.

Similarly, inconsistent results were seen for vision measurement (visual acuity) but most studies found small differences between people given NSAIDs and people not given NSAIDs.

Only one study reported quality of life, and this suggested little impact of NSAIDs on quality of life.

Adverse events mainly consisted of a burning or stinging sensation.

How up-to-date is this review?

The review authors searched for studies that had been published up to 2 September 2016.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

NSAIDs plus steroids compared with steroids for the prevention of macular oedema after cataract surgery

Patient or population: people having cataract surgery
Setting: eye hospital
Intervention: NSAIDs plus steroids
Comparison: steroids

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with steroids	Risk with NSAIDs plus steroids				
Poor vision due to MO at 3 months after surgery	74 per 1000	30 per 1000 (17 to 56)	RR 0.41 (0.23 to 0.76)	1360 (5 RCTs)	⊕⊕◯◯ LOW [12]	-
Poor vision due to MO at 12 months after surgery	20 per 1000	26 per 1000 (2 to 407)	RR 1.32 (0.09 to 20.37)	88 (1 RCT)	⊕◯◯◯ VERY LOW [13]	-
Quality of life at 3 months after surgery	See comment	-	-	74 (1 RCT)	-	Reported in 1 study only using COMTOL questionnaire. Data not fully reported but no significant differences in terms of quality of life, compliance and satisfaction scores
Central retinal thickness at 3 months after surgery; assessed with OCT	See comment	-	-	1021 (8 RCTs)	-	Trial results were inconsistent (I^2 = 87%). Results ranged from -30.9 microns in favour of NSAIDs plus steroids to +7.44 microns in favour

						of steroids alone
Adverse effects	See comment	-	-	(18 RCTs)	-	In general, no major adverse effects were noted. The main consistent observation was burning or stinging sensation with use of NSAID drops
MO at 3 months after cataract surgery, clinically symptomatic, assessed with OCT	130 per 1000	52 per 1000 (42 to 64)	RR 0.40 (CI 0.32 to 0.49)	3638 (21 RCTs)	⊕⊕◯◯ LOW [145]	
BCVA at 3 months after surgery; assessed with logMAR scale from: -1.3 to 1.3	See comment	-	-	1158 (10 RCTs)	-	Trial results were inconsistent (I^2 = 70%), but all except one study found differences less than 0.1 logMAR, i.e. clinically indistinguishable from no difference

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
__BCVA__: best corrected visual acuity; __CI:__ confidence interval; __MO__: macular oedema; __NSAID__: non-steroidal anti-inflammatory drug; __OCT__: optical coherence tomography; __RCT__: randomised controlled trial; __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 1 level for risk of bias: studies at unclear or high risk of bias.
[2] Downgraded 1 level for indirectness: extent of visual loss not always clearly defined.
[3] Downgraded 2 levels for imprecision: Only 2 events.
[4] Downgraded 1 level for publication bias: asymmetric funnel plot suggestive of publication bias.

[5] We considered downgrading an additional 1 level for indirectness as the MO was not always OCT-verified and it was not always clear if the MO was clinically symptomatic. However, we did not do so partly because the size of the effect was quite strong.

BACKGROUND

Description of the condition

Cataract refers to the clouding of the natural crystalline lens of the eye. It is the leading cause of avoidable visual impairment and blindness in the world. The World Health Organization (WHO) estimates that unoperated cataract alone accounts for 33% of visual impairment, an estimated 94 million cases worldwide (Pascolini 2012). In many parts of the world, particularly higher-income countries, availability of cataract surgery at a relatively early stage of visual impairment in the disease process has led to this procedure being one of the most commonly performed surgical procedures worldwide.

Macular oedema (MO) is the accumulation of extracellular fluid in the central retina (the macula) which may present following cataract surgery with lens implantation (pseudophakic macular oedema) or without (aphakic macular oedema) and may give rise to poor visual outcome with reduced visual acuity and distortion of the central vision. The diagnosis of this condition is made both clinically using slit lamp biomicroscopic examination of the macula and with the aid of fundus fluorescein angiography or optical coherence tomography (OCT) (Choi 2005).

The incidence of MO varies with type of surgery, intraoperative complications and pre-existing risk factors. Reported risk of MO varies between 0.9% and 5% for modern uncomplicated phacoemulsification cataract surgery (Spaide 1993), but can be as high as 10% in the presence of surgical complications such as vitreous loss (Blomquist 2002). Vision is not always affected, and the incidence of MO with decrease in visual acuity is reported at 1% (Ahmed 2013), and is associated with increasing retinal thickness (Hee 1995). A multicentre audit of 55,567 cataract operations in the UK's National Health Service (NHS) showed a risk of 1.62%, at a median postoperative review time of 31 days (Jaycock 2009). This was based on surgeons' reports rather than systematic examination of the macula and was defined as poor visual outcome attributed to MO.

Other risk factors for MO include ocular inflammatory diseases such as uveitis, retinal ischaemic conditions such as central and branch retinal vein conditions, retinal vascular diseases and dystrophies, for example retinitis pigmentosa and retinal telangiectasia, as well as degenerative causes such as age related macular degeneration and diabetic retinopathy while the use of topical prostaglandin analogue therapy in glaucoma remains a theoretical risk (Nelson 2003). The use of topical adrenaline 2% (epinephrine) in aphakic patients has also been described to be associated with macular oedema. Other factors may include cerebrovascular and cardiovascular disease (Jain 2001) but the pathogenesis is unclear.

MO is often self-limiting with spontaneous resolution (Ahmed 2013). The small proportion of patients with chronic persistent MO may be difficult to treat (Yannuzzi 1995), and they may experience permanent reduction in vision from atrophy of the photoreceptor layer of the retina (Ahmed 2013). Chronic oedema may lead to the formation of cystic spaces in the retina, termed 'cystoid macular oedema' (CMO).

Description of the intervention

The intervention is the topical use of non-steroidal anti-inflammatory drugs (NSAIDs), in this case, eyedrops, in addition to topical steroid eyedrops after cataract surgery. They may also be used preoperatively, primarily to reduce the risk of pupil constriction during surgery, but this may potentially also reduce the risk of MO. Non-steroidal anti-inflammatory agents are a group of drugs which are in common use orally as over-the-counter treatments for the reduction of pain, redness and swelling associated with systemic inflammation. Some of these are also available in eyedrop form as prescription medicines for the reduction of ocular inflammation.

The comparative intervention is the use of topical steroids on the eye after cataract surgery, which is current standard therapy, and may in itself reduce the risk of MO. Steroids are a group of prescription-only drugs which are used systemically to suppress the symptoms, signs and sequelae of inflammation. They are also used in their topical eyedrop form for the reduction of ocular inflammation.

In the last decade or so, several clinical trials have examined the use of topical NSAIDs in the treatment and prevention of postoperative inflammation and pseudophakic macular oedema, without the adverse effects of topical corticosteroids (Ballonzoli 2010; Carnahan 2000; Heier 1999; Polanski 1992; Solomon 2001). NSAIDs such as ketorolac and indomethacin are cyclo-oxygenase inhibitors which suppress breakdown of the blood-aqueous barrier that may occur in the early postoperative period (Flach 1987; Flach 1988; Miyake 1984; Sanders 1984).

Jain 2001 recommended the use of prophylactic NSAIDs in patients with predisposing factors to developing postsurgical MO, irrespective of cause. Other clinical studies suggest that topical NSAIDs may be more effective than topical steroids in re-establishing the blood-aqueous barrier postoperatively, suggesting an important role in MO prevention (Flach 1989; Kraff 1990; Ursell 1999).

The meta-analysis conducted in Rossetti 1998 of the use of NSAIDs suggested possible beneficial effects of NSAIDs for both the prophylaxis and treatment of MO, but concluded that the overall quality of the evidence was insufficient to justify recommendation of its widespread use in prophylaxis. A Cochrane Review on treatment of MO following cataract surgery, found that two out of seven included randomised controlled trials (RCTs) showed a beneficial effect of NSAIDs on chronic MO (Sivaprasad 2004), although problems with trial quality and heterogeneity prevented valid meta-analysis.

A recent randomised, placebo-controlled trial looking at the adjunctive effect of topical NSAIDs in addition to intravitreal

steroids (triamcinolone) and intravitreal anti-vascular endothelial growth factor (bevacizumab) in chronic MO, found a statistically significant improvement with the use of topical nepafenac in reduction of retinal thickness and improvement in visual acuity at 16 weeks (Warren 2010). NSAIDs have also been used with good tolerance and efficacy, as an alternate treatment for patients with MO of mixed origin who are steroid responders, and therefore cannot be treated with steroids (Warren 2008).

How the intervention might work

NSAIDs are cyclo-oxygenase inhibitors and may work by reducing the production of pro-inflammatory prostaglandins. Inflammation within tissue is caused by the production of pro-inflammatory products by several pathways. NSAIDs act to suppress the cyclo-oxygenase pathway of inflammation, inhibiting production of prostaglandins (Eisenach 2010).

Why it is important to do this review

As cataract surgery is the second most commonly performed operation worldwide, and MO occurs in between 1% and 10% of all cataract surgeries (depending on risk and complications) and leads to poor visual outcome, there is a significant volume of visual morbidity which can be potentially prevented if it is found that NSAIDs are effective in its prophylaxis. NSAIDs are relatively inexpensive, easily obtainable and carry the potential to significantly improve the outcome of cataract surgery worldwide.

Despite some evidence in favour of the beneficial effects of NSAIDs in MO, uncertainty remains about whether it has significant benefit in the prevention of MO when used perioperatively in addition to steroids. A recent editorial posed the question as to how prescribing NSAIDs for routine cataract surgery became so popular in the USA without compelling evidence of a visual benefit to patients (Kim 2016a). This uncertainty is reflected in widespread variation in clinical practice. For example, NSAIDs are much less frequently used in the UK for this indication. This review attempts either to resolve the persisting clinical uncertainty or to identify the need for further research to achieve such resolution.

This review is confined to addressing the use of NSAIDs in the prophylaxis of MO. A separate Cochrane Review on treatment of established cystoid macular oedema (CMO) has already been published (Sivaprasad 2004), but the effectiveness of NSAIDs in treatment remains uncertain. MO can lead to permanent structural damage in the central retina, therefore a prevention strategy may be more effective than treatment after the damage has been done.

OBJECTIVES

The aim of this review is to answer the question: is there evidence to support the prophylactic use of topical NSAIDs either in addition to, or instead of, topical steroids postoperatively to reduce the incidence of macular oedema (MO) and associated visual morbidity.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomised controlled trials (RCTs) in this review. We excluded within-person studies i.e. studies where eyes are randomly allocated to the intervention and comparator due to the possibility that the effect of non-steroidal anti-inflammatory drugs (NSAIDs) in one eye may affect the outcome in the other.

Types of participants

We included trials in which adult participants had undergone standard surgery for age-related cataract. We included participants irrespective of their baseline risk of MO, in particular, we included people with diabetes and uveitis.

Types of interventions

The primary comparison of this review was topical NSAIDs in addition to topical steroids versus topical steroids alone in cataract surgery. Surgery can include extracapsular cataract extraction (ECCE; large incision with sutures), manual small incision cataract surgery (MSICS; small incision without sutures), phacoemulsification cataract surgery (mechanised small incision extracapsular extraction) and intracapsular cataract extraction (ICCE; planned and unplanned intracapsular procedures).

We included trials of preoperative and/or postoperative topical NSAIDs in conjunction with postoperative topical steroids. The comparator was postoperative topical steroids alone.

A secondary comparison was preoperative and/or postoperative topical NSAIDs alone versus topical postoperative steroids alone.

We included studies irrespective of whether incident MO was subsequently treated.

Types of outcome measures

Primary outcomes

- The proportion of people with a poor vision outcome due to MO in the study eye at three months after surgery.

We defined poor vision outcome as best corrected visual acuity (BCVA) not improving to 6/9 or better (or equivalent with other notations of vision) attributed to a diagnosis of MO (detected clinically, angiographically or on optical coherence tomography (OCT)). This included participants who developed MO and required and received treatment.

Our primary outcome was measured at three months after surgery, which we took as any observation between one month and six months after surgery. We also examined poor visual outcome due to MO at 12 months after surgery, which we took as any observation between six and 18 months after surgery.

Secondary outcomes

- Any quality of life or patient satisfaction measure relating to the patient's experience of surgery on the study eye., at three months and 12 months after surgery
- Change in central retinal thickness from preoperative assessment in the study eye, at three months and 12 months after surgery, as measured by OCT scan. If change in central retinal thickness was not available we used the final value.

Adverse effects

We looked at known harms of NSAIDs including respiratory effects and gastrointestinal disturbance, in addition to intolerance of medication and allergic reactions. We recorded any other harms such as liver toxicity, as has been reported with some NSAIDs.

Resource use and costs

In our protocol (Abeysiri 2011) we planned to look at economic evaluations of the cost-effectiveness and cost per quality-adjusted life year (QALY)/disability-adjusted life year (DALY) modelling. We amended this to look at resource use and costs more generally.

Additional outcomes (National Institute for Health and Care Excellence (NICE))

We collected data on the following additional outcomes as part of our collaboration with NICE.

- Macular oedema (MO) (clinically symptomatic, OCT-verified).
- Inflammation.
- BCVA.

Search methods for identification of studies

Electronic searches

We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (2016, Issue 8), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to September 2016), Embase (January 1980 to September 2016), Latin American and Caribbean Health Sciences Literature Database (LILACS) (1982 to September 2016), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 2 September 2016.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), Embase (Appendix 3), LILACS (Appendix 4), ISRCTN (Appendix 5), ClinicalTrials.gov (Appendix 6), and the ICTRP.

Searching other resources

We searched the reference lists of the studies included in the review. We used the Science Citation Index to find studies that have cited the individual trials. We did not handsearch conference proceedings or journals specifically for the review.

Data collection and analysis

Selection of studies

Three review authors (CL, BL, DL) screened the titles and abstracts resulting from the searches independently. We obtained full copies of the potentially relevant trials. Three review authors (CL, BL, DL) independently assessed full copies for inclusion according to the 'Criteria for considering studies for this review.' We resolved disagreements by discussion.

We listed all excluded studies and provided a brief justification for exclusion (See Characteristics of excluded studies).

Data extraction and management

Four review authors (JE, CL, DL, BL) independently extracted data using a pre-piloted data extraction template in Covidence (Covidence 2016). A fifth review author (CB) generated a random sample of 20% of studies and checked data input for these. We resolved discrepancies by discussion.

We collected the following information on study characteristics (Appendix 8).

- Study design: parallel group RCT, one or both eyes included and/or reported.
- Participants: country, total number of participants, age, sex, inclusion and exclusion criteria.
- Intervention and comparator details: including number randomised to each.

- Primary and secondary outcomes as measured and reported in the trials, adverse events, methods of measurement (e.g. which chart is used for visual acuity assessment, which OCT scanner was used).
- Length of follow-up.
- Date study conducted.
- Funding and conflicts of interest reported.
- Trial registration number.

We collected data on our predefined outcomes separately for intervention and comparator groups. For multi-arm studies we planned to use data relevant to our intervention and comparator groups. If two groups contain relevant data (for example, if pre/postoperative application of NSAIDs) we combined groups using the RevMan calculator (RevMan 2014).

As far as possible, we extracted data for an intention-to-treat (ITT) analysis. We contacted trial investigators as needed. Data were imported directly from Covidence into Review Manager 5 by JE (RevMan 2014), and checked by the other review authors (CL, DL, BL). CB then conducted a final random assessment.

Assessment of risk of bias in included studies

We used Cochrane's 'Risk of bias' tool for assessing risk of bias in each included study. Four review authors (JE, CL, DL, BL) independently assessed risk of bias according to methods set out in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We followed the specific rules as set out in Table 1 and resolved disagreements by discussion.

We contacted trial investigators for Miyake 2011 for clarification of random allocation.

Measures of treatment effect

We calculated the risk ratio for outcome measures reported as dichotomous data (for example, poor visual acuity attributed to MO within three months). We calculated the mean difference for measures of retinal thickness. We planned to analyse ordinal outcome data as dichotomous data if an established defensible cut-off point is available, such as quality of life measures. We did not plan to meta-analyse adverse effects.

Unit of analysis issues

Trials included may randomise one or both eyes to the intervention or comparator. If both eyes were allocated to the same treatment, we planned to analyse as 'clustered data' if data were available. In the event four trials included data on both eyes, but this was generally a small proportion of the total participants. We have analysed as reported. We excluded studies which allocated different eyes to different treatments as there may be a confounding cross-over effect due to systemic absorption.

Dealing with missing data

We assessed all included trials for number of participants excluded or lost to follow-up. We documented reasons for loss to follow-up by treatment group, if reported. We aimed to do an ITT analysis for included trials using imputed data; if computed by the trialists we did not plan to impute missing data on their behalf.

Assessment of heterogeneity

Where heterogeneity was observed between individual study results we did not combine studies but present a tabulated summary of results. We did not rely on statistical significance of a Chi^2 test to indicate heterogeneity but examined the forest plot of the study results and the overall characteristics of the studies. We looked at the consistency between studies by examining the I^2 statistic value. We considered I^2 values over 50% to indicate substantial inconsistency, but we also considered the direction of effects.

Assessment of reporting biases

We considered selective outcome reporting under the risk of bias assessment (Table 1). We planned to look at funnel plots and consider tests for asymmetry for bias assessment in the event of 10 or more trials contributing data to a meta-analysis.

Data synthesis

We aimed to use a random-effects model provided we did not detect substantial inconsistency between individual study results. If there were fewer than three trials in a comparison we planned to use the fixed-effect model. Where heterogeneity was observed between studies (see Assessment of heterogeneity) we did not combine studies but presented a narrative summary of results.

'Summary of findings' table

We prepared a 'Summary of findings' table presenting relative and absolute risks. We graded the overall certainty of the evidence for each outcome using the GRADE classification (Atkins 2004). We considered the following: risk of bias of included studies, precision of the effect estimate, consistency of effects between studies, directness of the outcome measure and publication bias. JE did the assessment and this was checked by other authors. We included the following outcomes in the 'Summary of findings' tables.

1. Poor vision outcome due to MO at three months after surgery.
2. Poor vision outcome due to MO at 12 months after surgery.
3. Quality of life at three months after surgery.
4. Central retinal thickness at three months after surgery.
5. Adverse effects.
6. MO (clinically symptomatic, OCT-verified) at three months after surgery
7. BCVA at three months after surgery.

Subgroup analysis and investigation of heterogeneity

We planned to conduct a subgroup analysis on the primary outcome comparing the effect of treatment on people with higher baseline risk of MO (diabetes/uveitis) with people with lower risk of MO (no diabetes/uveitis), but we did not do them as planned as there were not enough data on the primary outcome.

Sensitivity analysis

We planned to perform three sensitivity analyses on the primary outcome, but we did not do them as planned as there were not enough data on the primary outcome.

- Excluding studies at high risk of bias in one or more domains.
- Excluding industry-funded studies.
- Comparing fixed-effect and random-effects models (if three or more trials).

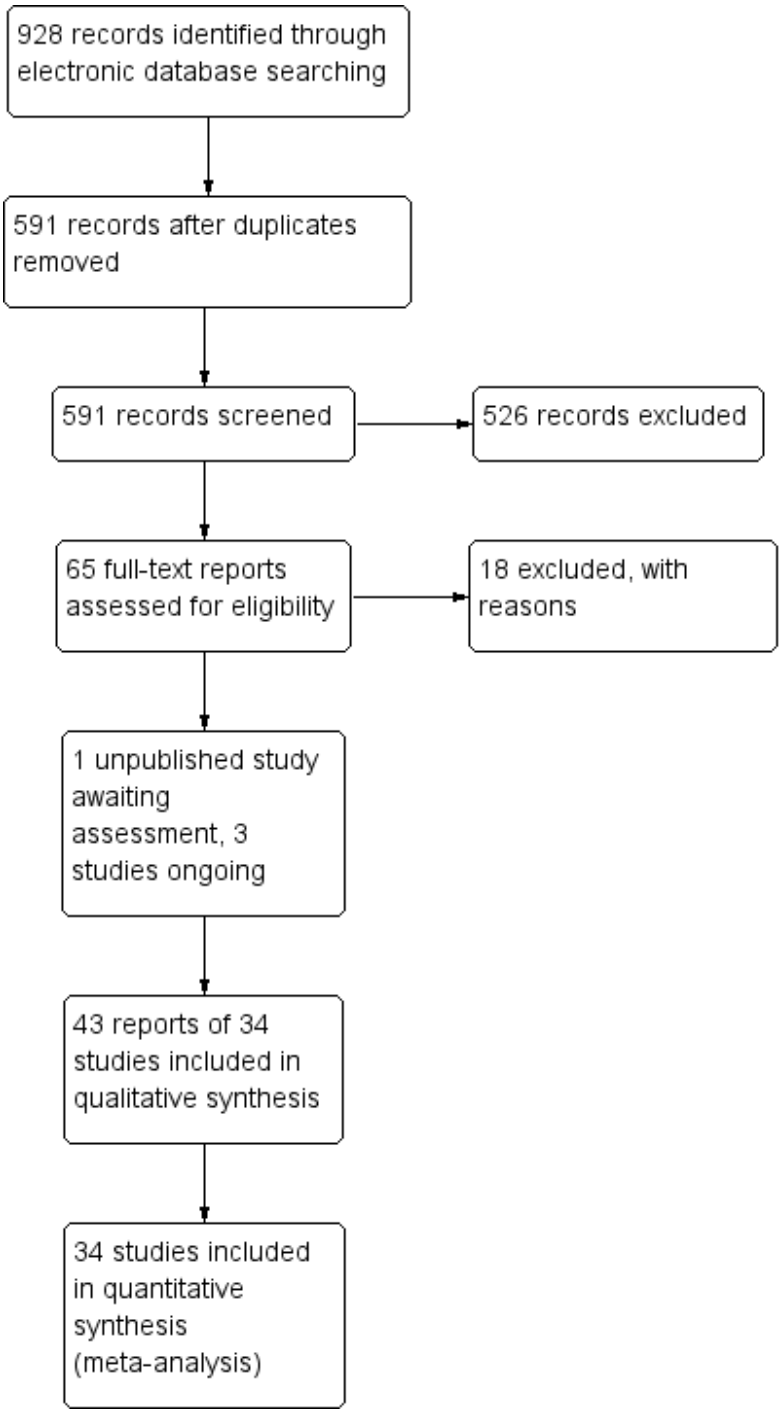
RESULTS

Description of studies

Results of the search

The electronic searches yielded a total of 928 references (Figure 1). The Cochrane Information Specialist removed 337 duplicate records and we screened the remaining 591 reports. We rejected 526 records after reading the abstracts and obtained the full-text reports of 65 references for further assessment. We identified 43 reports of 34 studies which met the inclusion criteria (see Characteristics of included studies for details), and excluded 18 reports of 18 studies (see Characteristics of excluded studies for details). One unpublished trial is currently awaiting assessment (CTRI/2009/091/001078). We identified three ongoing studies (NCT01694212; NCT01774474; NCT02646072).

Figure 1. Study flow diagram.



Included studies

We have summarised the characteristics of the 34 included studies below. Details for individual studies can be found in the Characteristics of included studies. The information is also summarised in Table 2; Table 3; Table 4; Table 5; Table 6

Setting and conduct of Study

See Table 2.

The studies were conducted in Brazil (Ticly 2014; Tzelikis 2015), Canada (Almeida 2008; Almeida 2012; Solomon 1995), China (Li 2011; Wang 2013; Zhang 2008), Egypt (Elsawy 2013), Germany (Quentin 1989; Solomon 1995), Greece (Chatziralli 2011; Moschos 2012) , Italy (Italian Diclofenac Study Group 1997; Rossetti 1996), Japan (Asano 2008; Endo 2010; Miyake 2007; Miyake 2011; Miyanaga 2009), Mexico (Cervantes-Coste 2009), South Korea (Jung 2015), Sweden (Zaczek 2014), Switzerland (Umer-Bloch 1983), Turkey (Tunc 1999; Yavas 2007) and the USA (Brown 1996; Donnenfeld 2006; Kraff 1982; Mathys 2010; Singh 2012; Tauber 2006; Wittpenn 2008; Yannuzzi 1981; Yung 2007).

They were all parallel group RCTs, i.e. participants were randomly allocated to intervention or comparator. Three of the studies were described as "open-label" (Almeida 2008;; Endo 2010; Wang 2013).

Four studies were funded by industry alone (Brown 1996; ; Solomon 1995; Tauber 2006; Wittpenn 2008;); seven studies reported only non-industry funding (Almeida 2008; Almeida 2012; Jung 2015; Kraff 1982; Mathys 2010; Wang 2013; Yannuzzi 1981); two studies had funding from both industry and non-industry sources (Donnenfeld 2006; Zaczek 2014) and the rest of the studies did not report the source of funding.

Declarations of interest were not reported in 12 studies; 17 studies reported that they had no conflicts of interest and six studies reported conflicts of interest for one or more investigators (Donnenfeld 2006; Italian Diclofenac Study Group 1997; Miyake 2011; Singh 2012; Tauber 2006; Wittpenn 2008).

Six trials were registered on a publicly available database. For three of these trials the registration was probably prospective as the month of registration was the same, or before, the month the study started (Almeida 2008; Mathys 2010; Singh 2012).Three trials were registered retrospectively (Almeida 2012; Tzelikis 2015; Wittpenn 2008).

Two trials were reported in abstract form only (Tauber 2006; Yung 2007). However, we contacted the first authors of Tauber 2006 and Yung 2007 and we received additional information in the form of a poster from Yung 2007.

Participants

See Table 3 and Table 4.

There were variations in the reporting of recruited and randomised participants. As such it is difficult to establish definitively the total number of people that were randomised in these trials. We estimate that there were 5532 people (5608 eyes) enrolled in these 34 studies and 4476 followed up. (Table 3).

Five studies did not report the number of people randomised (Brown 1996; Tauber 2006; Umer-Bloch 1983; Yannuzzi 1981; Zhang 2008). For four of these five studies we estimated the number of people in the trial from the number analysed. One study provided no information on the number of participants (Brown 1996).

For those studies that did not report follow-up clearly we have assumed the number randomised and number followed up was the same.

The majority of the studies (n = 24) enrolled one eye person in the trial, although this was not always clearly described. In six studies the number of eyes/people was not reported in enough detail to be confident how many eyes per person had been enrolled (Donnenfeld 2006; Kraff 1982; Tauber 2006; Umer-Bloch 1983; Wang 2013; Yung 2007), although it is likely that they too largely performed unilateral surgery.

Four studies performed bilateral surgery on a subset of patients, and so had more eyes than people in the trial (Almeida 2008; Elsawy 2013; Yannuzzi 1981; Zhang 2008). The proportion of people with bilateral surgery was 1% (Yannuzzi 1981), 8% (Almeida 2008), 11% (Zhang 2008) and 23% (Elsawy 2013). None of the studies adjusted for within-person correlation. We have analysed the data as reported.

For the studies that reported average age, the median average age of participants was 70 years (Table 4). Ages ranged from 37 to 100 years. For the studies that reported gender, the median percentage of women was 54%.

Fifteen studies reported that they excluded patients with diabetes or diabetic retinopathy, or were a "low risk population". Nine studies did not report the diabetes status of their participants. Nine studies included people with diabetes and reported the percentage of the participants with diabetes. The percentage with diabetes was 10%/9% (Chatziralli 2011; Miyake 2011), 21%/20% (Almeida 2008; Cervantes-Coste 2009) and 26% (Jung 2015). Five studies only included people with diabetes (Elsawy 2013; Endo 2010; Li 2011; Singh 2012; Yung 2007).

The majority of studies either excluded people with uveitis (n = 19) or had a "low risk population" (Almeida 2012), or very low proportion with uveitis (1/56 people) (Almeida 2008). Thirteen studies did not report uveitis and it was not included in the exclusion criteria.

Interventions

See Table 5

Type of surgery

Twenty-four of the 34 studies reported that only phacoemulsification was performed for cataract extraction (Table 5). In one study both extracapsular cataract extraction (ECCE) and phacoemulsification were performed (Kraff 1982). Four studies reported that they performed ECCE (Italian Diclofenac Study Group 1997; Rossetti 1996; Solomon 1995; Tunc 1999), two studies performed ICCE (Quentin 1989; Yannuzzi 1981) and one study performed a mixture of ECCE/intracapsular cataract extraction (ICCE) (Umer-Bloch 1983). In two studies that were reported in abstract form only there was no information on type of surgery but we have assumed that they used phacoemulsification because of the date published and location of the study (Tauber 2006; Yung 2007).

Comparison

Twenty-eight of the 34 studies compared non-steroidal anti-inflammatory drugs (NSAIDs) with steroids versus steroids. In 14 of these 28 studies, a placebo (for the NSAIDs) was used in the comparator group. This placebo was not specified in two trials (Quentin 1989; Rossetti 1996;); was artificial tears in five trials (Ticly 2014; Tzelikis 2015; Wittpenn 2008; Yung 2007; Zaczek 2014); a vehicle in six studies (Donnenfeld 2006; Kraff 1982; Singh 2012; Solomon 1995; Umer-Bloch 1983; Yannuzzi 1981); and sterile saline drops in Almeida 2012. .

Six of the 34 studies compared NSAIDs (on their own) with steroids (Asano 2008; Brown 1996; Endo 2010; Italian Diclofenac Study Group 1997; Miyake 2007; Miyake 2011). Only one of these studies used a placebo in the steroid group; the contents of this placebo were not specified. (Italian Diclofenac Study Group 1997).

NSAIDs

The most frequently used NSAID was ketorolac (11 studies) followed by diclofenac (9 studies), nepafenac (7 studies), indomethacin (5 studies), bromfenac (4 studies), pranoprofen (1 study) and flurbiprofen (1 study). Four studies had two different NSAID groups - ketorolac and nepafenac (Almeida 2012; Tzelikis 2015), ketorolac and bromfenac (Jung 2015) and flurbiprofen and indomethacin (Solomon 1995). We combined these groups for the analysis.

The ketorolac concentration was either 0.4% or 0.5%. Diclofenac was largely used at a concentration of 0.1% (7 studies) but also used at 1% in Li 2011 and concentration was not specified in one study (; Rossetti 1996). Nepafenac was used at 0.1% in six studies and 1% in one study (Singh 2012). Indomethacin 1% was used in three studies (Solomon 1995; Umer-Bloch 1983; Yannuzzi 1981), 0.1% in Yavas 2007 while the concentration used was not specified in Kraff 1982. Bromfenac 0.1% was used in Miyanaga 2009, Jung 2015 and Wang 2013; it was not specified in Endo 2010. Flubiprofen was used at 0.03% (Solomon 1995). Pranopfen concentration was not specified (Zhang 2008).

Steroids

Prednisolone was used in 13 studies, usually at 1%.

Dexamethasone was used in 15 studies, at a concentration of 0.1% in eight studies and 1% in one study (Tunc 1999). The concentration used was not specified in 6 studies. It was combined with tobramycin in four studies (Cervantes-Coste 2009; Li 2011; Rossetti 1996; Zhang 2008) and other antibiotics (Kraff 1982; Moschos 2012; Umer-Bloch 1983).

Betamethasone was used at 0.1% in two studies (Asano 2008; Miyanaga 2009) and not specified in one study (Endo 2010).

Fluorometholone 0.1% was used as the sole topical corticosteroid therapy in three studies (Miyake 2007; Miyake 2011; Wang 2013) and used as part of a tapering regimen in one study (Kraff 1982).

The type of steroids used in Yannuzzi 1981 were not specified.

Other medications

Most studies reported the use of additional antibiotics. See Characteristics of included studies.

Outcomes

Maximum follow-up ranged from one month (8 studies) to 12 months postoperatively (Kraff 1982; Yannuzzi 1981) (Table 6).

The majority of trials followed up to two months or less (23 studies). Five studies followed up to three months (Elsawy 2013; Singh 2012; Umer-Bloch 1983; Yavas 2007; Yung 2007) and six studies followed up longer: 140 days (Italian Diclofenac Study Group 1997), six months (Quentin 1989; Rossetti 1996; Solomon 1995) and 12 months (Kraff 1982; Yannuzzi 1981). Kraff 1982 had a low follow-up of 10 % at 12 months

Table 6 shows the outcomes reported in the studies.

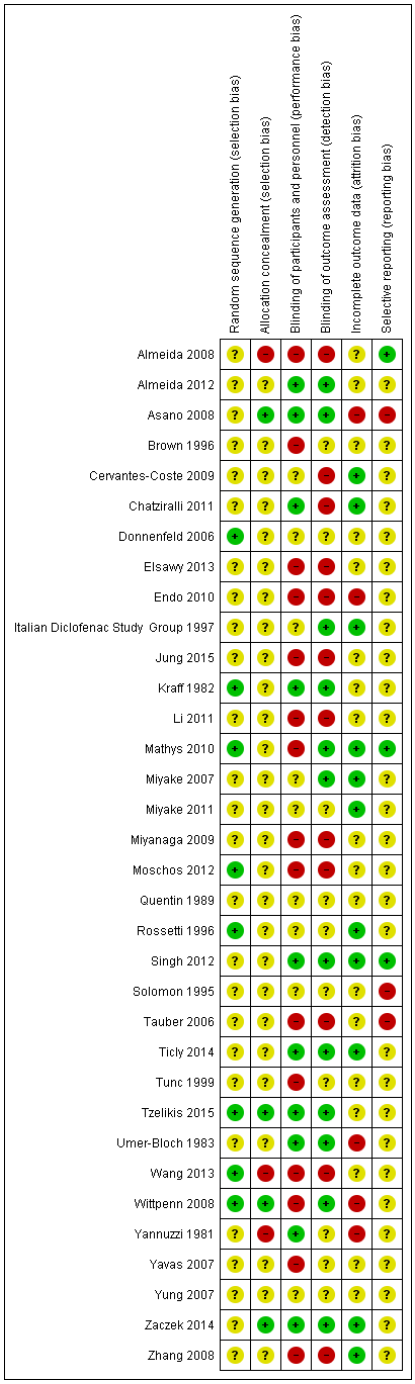
Excluded studies

See Characteristics of excluded studies.

Risk of bias in included studies

See Figure 2

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



Allocation

The majority of trialists did not report sufficient information to judge selection bias. These trials were marked as unclear for sequence generation and allocation concealment. Only two trials were judged at low risk of bias on both sequence generation and allocation concealment (Tzelikis 2015; Wittpenn 2008).

Eight trials reported a method of sequence generation judged to be likely to generate an unpredictable sequence. Some trials used random number tables (Kraff 1982; Rossetti 1996; Wang 2013), other reports suggested computer-generated random numbers or allocation schedules (Mathys 2010; Tzelikis 2015), others referred to random numbers or randomly generated lists but did not specify how these were created (Donnenfeld 2006; Moschos 2012; Wittpenn 2008).

Four trials reported a convincing method of allocation concealment (Asano 2008; Tzelikis 2015; Wittpenn 2008; Zaczek 2014). In Asano 2008 the assignment code was kept secret by a named individual until the end of the study; in Tzelikis 2015 all investigators were masked to treatment group; Wittpenn 2008 used a central co-ordination centre for allocation and in Zaczek 2014 the allocation was prepared in such a way that neither investigators nor participants could identify the group.

In three studies, we judged that the allocation was probably not concealed adequately (Almeida 2008, Wang 2013; Yannuzzi 1981).

Blinding

Ten studies were not masked and we judged them to be at high risk of both performance and detection bias (Almeida 2008; Elsawy 2013; Endo 2010; Jung 2015; Li 2011; Miyanaga 2009; Moschos 2012; Tauber 2006; Wang 2013; Zhang 2008).

Eight studies were masked and we judged them to be at low risk of both performance and detection bias (Almeida 2012; Asano 2008; Kraff 1982; Singh 2012; Ticly 2014; Tzelikis 2015; Umer-Bloch 1983; Zaczek 2014).

Two studies that did not mask participants, stated explicitly that outcome assessors were masked (Mathys 2010; Wittpenn 2008).

For six studies, there was not enough information to judge the risk of either performance or detection bias (Donnenfeld 2006; Miyake 2011; Quentin 1989; Rossetti 1996; Solomon 1995; Yung 2007).

Incomplete outcome data

We judged five studies to be at high risk of attrition bias. In Asano 2008, there was variable follow-up by outcome, and it was not clearly explained why. Some of the stated exclusion criteria for the study, such as inflammation after surgery, would have been related to the outcome. In Endo 2010, follow-up was unequal between study groups and reason for loss to follow-up was not clearly reported. In Umer-Bloch 1983, 35 people withdrew before the end of the study because of intraoperative complications or they had, as only later recognised, an exclusion criteria as defined as maculopathy, diabetic retinopathy, prior uveitis or a systemic steroid therapy. It was not reported to which groups these patients belonged. In Wittpenn 2008, there was very low follow-up at six weeks, with 77/546 (14%) people followed-up. In Yannuzzi 1981 there was a high loss to follow-up at 12 months: 38/100 (38%) in the NSAIDs group and 50/131 (38%) in the control group were followed-up.

We judged 11 studies to be at low risk of attrition bias. For the other studies there was not enough information to judge.

Selective reporting

For most studies there was little information to judge selective outcome reporting because we did not have access to a trial registry entry or study protocol. We judged three studies to be at low risk of selective outcome reporting on the basis that the trial was prospectively registered and all outcomes prespecified on the clinical trials registry entry were reported (Almeida 2008; Mathys 2010; Singh 2012). For three studies it was clear that some outcomes were not fully reported and so we judged them to be at high risk of selective outcome reporting bias (Asano 2008; Solomon 1995; Tauber 2006).

Effects of interventions

See: **Summary of findings for the main comparison** NSAIDS plus steroids compared with steroids for the prevention of macular oedema after cataract surgery; **Summary of findings 2** NSAIDS compared with steroids for the prevention of macular oedema after cataract surgery

Non-steroidal anti-inflammatory drugs plus steroids versus steroids

Primary outcome

Poor vision due to macular oedema

Five studies reported this outcome at three months (eyes = 1360) (Analysis 1.1). Follow-up ranged from four weeks to two months. Two studies reported optical coherence tomography (OCT)-confirmed macular oedema (MO) with visual acuity < 6/9 in one study (Wittpenn 2008) but the level of visual impairment not defined

in the other (Wang 2013). Solomon 1995 defined the presence of clinical MO as visual acuity <=20/40 and angiographic evidence of CMO. Cervantes-Coste 2009 reported that none of the participants developed clinically significant macular oedema nor vision loss. Chatziralli 2011 reported that none of the participants developed clinically significant CMO as assessed via fundoscopy and the Amsler grid test. There was some evidence of selective reporting in Solomon 1995, which provided most of the information for the meta-analysis. Data were only reported for the earlier follow-up at days 21 to 60. Quote: "By day 121-240 the incidence of clinical CME [cystoid macular edema] was less than 2% in all three groups and no significant differences were seen."

People receiving non-steroidal anti-inflammatory drugs (NSAIDs) combined with steroids had a lower risk of poor vision due to macular oedema (MO) at three months after surgery compared with people receiving steroids alone. The pooled risk ratio (RR) was 0.41, 95% confidence interval (CI) 0.23 to 0.76; eyes = 1360; studies = 5. There was no evidence of any major inconsistency (I^2 = 5%). We judged this to be low-certainty evidence (Summary of findings for the main comparison). We downgraded for risk of bias, as the trials were poorly reported and were largely at high or unclear risk of bias. We downgraded for indirectness, as the outcomes reported by the trials only approximated the outcome which we wished to collect, which was poor vision (best corrected visual acuity (BCVA) < 6/9) due to MO.

One study reported this outcome at 12 months (Yannuzzi 1981). There was high attrition in this study (only 38% of eyes followed up) and only two events (RR 1.32, 95% CI 0.09 to 20.37; eyes = 88). We judged this to be very low-certainty evidence, downgrading for risk of bias and imprecision (2 levels; Summary of findings for the main comparison).

Secondary outcomes

Quality of life/patient satisfaction

One study reported quality of life at 1 month after surgery using the Comparison of Ophthalmic Medications for Tolerability (COMTOL) questionnaire (Almeida 2012), No differences in the impact upon quality of life measures were identified between the treatment and control groups. The use of topical NSAIDs was also reported to have good tolerability and comparable side-effect profile to placebo. However the data in this study were not fully reported and a response rate of only 60% was achieved with significant attrition with 65 out of 162 patients declining to answer the interview after surgery for "logistical reasons".

Quote: "The global [health-related quality of life] HRQOL questions showed no difference in the extent to which quality of life was affected by medication side effects between "not at all" and any reported effect (question 6; P = 0.8476). Regarding the extent quality of life was affected by activity limitations, there was no difference between "not at all" and any reported limitations (question 9; P = 0.8584). According to the COMTOL questionnaire, there was no difference in compliance between the 3 study groups (question 10; P = 0.3801). Most patients in all 3 groups reported being satisfied with the medication, and there was no difference between satisfied responses and dissatisfied responses (question 11; P = 0.4777)").

Central retinal thickness

Nine studies reported this outcome (eyes = 1112) (Analysis 1.2). Follow-up ranged from one to two months. Six studies reported central retinal thickness at the end of the follow-up period, three studies reported change in thickness from baseline. Trial results were inconsistent (I^2 = 87%). Results ranged from -30.9 µm in favour of NSAIDs plus steroids to +7.44µm in favour of steroids alone (Summary of findings for the main comparison).

Six studies reported change in macular volume (eyes = 570) (Analysis 1.3). The pooled mean difference (MD) was -0.14 mm^3 (95% CI -0.21 to -0.07). There was some inconsistency (I^2 = 50%), mainly attributable to Mathys 2010.

Adverse effects

See Table 7. In the studies that reported adverse effects, no evidence of serious adverse events were seen. The most notable adverse effect associated with NSAID use was burning or stinging sensation.

Resource use and costs

None of the studies commented on this.

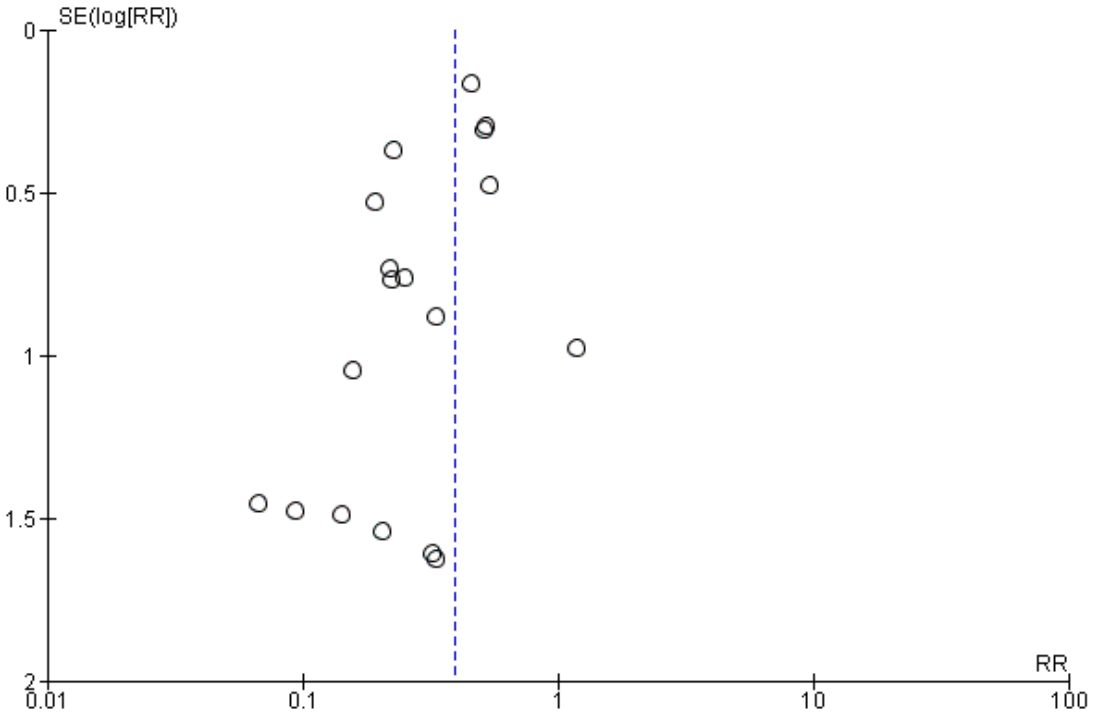
Additional National Institute for Health and Care Excellence (NICE) outcomes

Macular oedema (MO) (clinically symptomatic, optical coherence tomography-verified)

Twenty-one studies reported this outcome (eyes = 3638) (Analysis 1.4). Follow-up ranged from two weeks to just less than six months. Most studies reported "cystoid" macular oedema but it was not always clearly defined nor was it clear that it was clinically significant. Nine studies used OCT, although it was not always clear if the OCT was used to verify the MO; nine studies used fluorescein angiography, often using the Miyake 1977 classification; clinical assessment for the presence of MO was made in two studies.

There was an asymmetric funnel plot, suggesting that publication bias might be an issue (Figure 3).

Figure 3. Funnel plot of comparison: 1 NSAIDs plus steroids versus steroids, outcome: 1.4 Macular oedema.



People receiving NSAIDs combined with steroids had a lower risk of MO after surgery compared with people receiving steroids alone. The pooled RR was 0.40, 95% CI 0.32 to 0.49; I^2 = 0%. We judged this to be low-certainty evidence (Summary of findings for the main comparison). We downgraded one level for risk of bias, as the studies were at unclear or high risk of bias and we downgraded one level for publication bias as an asymmetric funnel plot was suggestive of publication bias. We considered downgrading one level for indirectness, as the MO was not always OCT-verified and it was not always clear if the MO was clinically significant but in the event did not as the size of the effect was strong.

Inflammation

Three studies reported inflammation as a dichotomous outcome (Analysis 1.5). In Cervantes-Coste 2009 there were no cases of "inflammatory cells greater than 1+ during first week of postoperative visits." In Chatziralli 2011, at day 28, inflammation, which was defined as corneal oedema or Tyndall reaction or conjunctival hyperemia was seen in two participants in the NSAIDs plus steroid group (RR 4.86, 95% CI 0.24 to 99.39); by day 35 this had disappeared. In Zhang 2008, 20 participants in the steroids group had inflammation defined as "Tyn granule +" compared to 0 participants in the NSAIDs plus steroids group at one month (RR 0.02, 95% CI 0.00 to 0.38). In view of such different results, we did not pool the data from these trials.

Two studies reported flare in photons/millisecond (eyes = 216) (Analysis 1.6). The MD was -1.41 photons/millisecond in favour of NSAIDs plus steroids (95% CI -2.30 to -0.52), but there was some inconsistency between the two studies (I^2 = 49%). There was some evidence of skew for the control group of Miyanaga 2009 (mean/standard deviation (SD) < 2).

Jung 2015 reported "summed ocular inflammation score" which was the sum of the scores of cells and flare, scored against a maximum total score of 9. The inflammatory score at one month was 0.21 ± 0.42 in the bromfenac group and 0.32 ± 0.48 in the ketorolac group (P = 0.853). The score in the control group was 0.84 ± 0.76.

Best corrected visual acuity

Ten studies reported BCVA (eyes = 1158) (Analysis 1.7). For Mathys 2010 change in BCVA was reported in letters. We converted this to logMAR score by multiplying by -0.02 and we estimated the SD from the P value.

There was statistical heterogeneity (I^2 = 70%), and not all effect estimates were in the same direction, so we did not provide a pooled estimate. However, we note that most studies found differences

clinically indistinguishable from no difference.

Non-steroidal anti-inflammatory drugs versus steroids

Primary outcome

Poor vision due to macular oedema

None of the studies reported this outcome.

Secondary outcomes

Quality of life/patient satisfaction

None of the studies reported this outcome.

Central retinal thickness

Two studies reported central retinal thickness (Analysis 2.1). The pooled MD was -22.64 µm (95% CI -38.86 to -6.43; I^2 = 0%) in favour of NSAIDs. We judged this to be low-certainty evidence (Summary of findings 2). We downgraded one level for risk of bias, as the studies were at unclear or high risk of bias, and we downgraded one level for imprecision as the confidence intervals include a clinically unimportant effect.

Adverse effects

See Table 7. In the studies that reported adverse effects, no evidence of serious adverse events were seen. The most notable adverse effect associated with NSAID use was burning or stinging.

Resource use and costs

None of the studies commented on this.

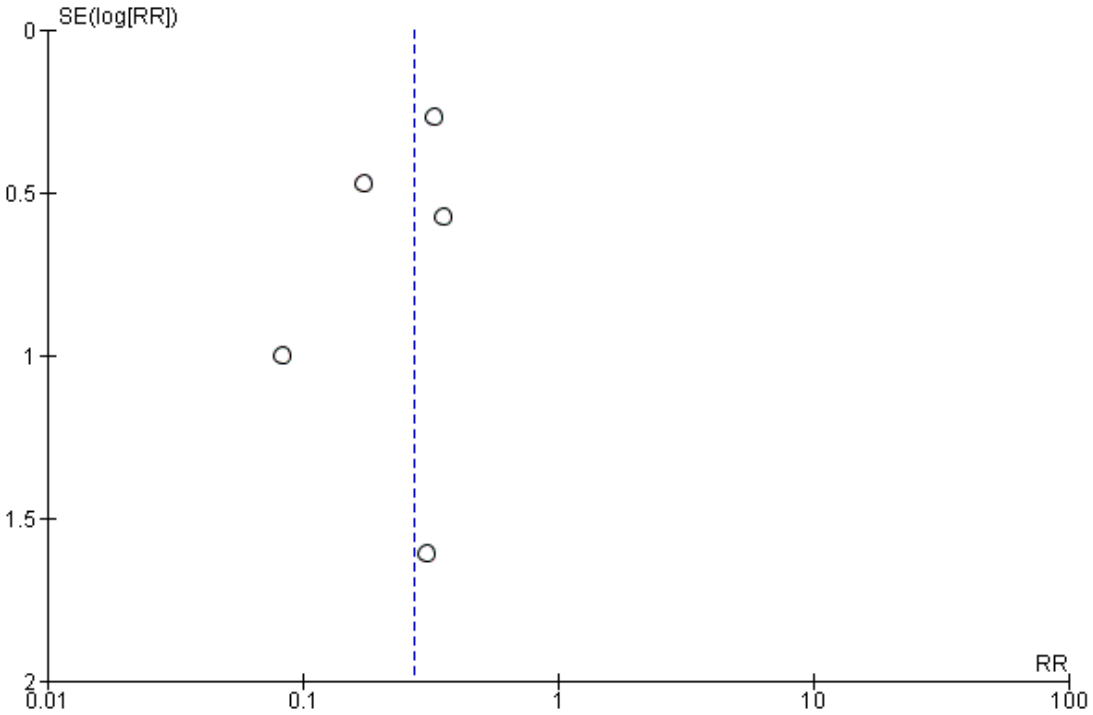
Additional NICE outcomes

Macular oedema (clinically symptomatic, optical coherence tomography-verified)

Five studies reported this outcome (eyes = 520) (Analysis 2.2). All studies assessed MO using fluorescein angiography. The pooled RR was 0.27 (95% CI 0.18 to 0.41) in favour of NSAIDs. We note that for Asano 2008 there may have been selective reporting - data on MO were reported only at five weeks, but were not reported at the end of eight weeks follow-up in that study.

We judged this to be low-certainty evidence (Summary of findings 2). We downgraded one level for risk of bias, as the studies were at unclear or high risk of bias and we downgraded one level for publication bias because of an asymmetric funnel plot suggestive of publication bias (Figure 4). We would not usually do a funnel plot with so few studies, but as the funnel plot for this outcome, for the comparison NSAIDs plus steroids versus steroids alone was asymmetric (Figure 3), we felt that publication bias may be an issue here as well.

Figure 4. Funnel plot of comparison: 2 NSAIDs versus steroids, outcome: 2.2 Macular oedema.



Inflammation

Five studies reported aqueous flare (eyes = 346) (Analysis 2.3). There was substantial inconsistency (I^2 = 68%) and some evidence of skewed data so we did not report a pooled value.

Best corrected visual acuity

Three studies reported BCVA (eyes = 220) (Analysis 2.4). There was statistical heterogeneity (I^2 = 84%) so we did not report a pooled value, but we note that all three studies found between group differences that were clinically indistinguishable from no difference.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

NSAIDscompared with steroids for the prevention of macular oedema after cataract surgery

Patient or population: people having cataract surgery
Setting: eye hospital
Intervention: NSAIDs
Comparison: steroids

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with steroids	Risk with NSAIDs				
Poor vision outcome due to MO at 3 months after surgery	-	-	-	-	-	No data were available for this outcome.
Poor vision outcome due to MO at 12 months after surgery	-	-	-	-	-	No data were available for this outcome.
Quality of life at 3 months after surgery						No data were available for this outcome.
Central retinal thickness at 3 months after surgery; assessed with OCT	The mean central retinal thickness at 3 months after surgery was 228 microns	MD 22.64 microns lower (38.86 lower to 6.43 lower)	-	121 (2 RCTs)	⊕⊕◯◯ LOW [14]	-
Adverse effects	-	-	-	488 (4 RCTs)	-	1 study had 2 unspecified complications in 142 participants, 2 studies reported that no adverse events were noted in either group, 1 study (55 people) men-

						tioned 15 mild adverse effects but unclear if related to treatment
MO at 3 months after cataract surgery; clinically symptomatic assessed with OCT	130 per 1000	35 per 1000 (23 to 53)	RR 0.27 (0.18 to 0.41)	520 (5 RCTs)	⊕⊕◯◯ LOW [123]	
BCVA at 3 months after surgery; assessed with logMAR scale from: -1.3 to 1.3	See comment	-	-	220 (3 RCTs)	-	Trial results were inconsistent (I^2 = 84%), but all studies found differences less than 0.1 logMAR, i.e. clinically indistinguishable from no difference.

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
__BCVA__: best corrected visual acuity; __CI:__ confidence interval; __MD__: mean difference; __MO__: macular oedema; __NSAID__: non-steroidal anti-inflammatory drug; __OCT__: optical coherence tomography; __RCT__: randomised controlled trial; __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 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 1 level for risk of bias: studies at unclear or high risk of bias.
[2] Downgraded 1 level for publication bias: asymmetric funnel plot suggestive of publication bias.
[3] We considered downgrading 1 level for indirectness as the MO was not always OCT-verified and not always clear if it was clinically symptomatic however we did not do so, partly because the effect was strong.
[4] Downgraded 1 level for imprecision: confidence intervals include clinically unimportant effect.
[5] Downgraded 1 level for inconsistency.

DISCUSSION

Summary of main results

See Summary of findings for the main comparison; Summary of findings 2.

We identified 34 studies that were conducted in the Americas, Europe, the Eastern Mediterranean region and South-East Asia.

Over 5000 people were randomised in these trials. The majority of studies probably enrolled one eye per participant, a small subset (4 trials) enrolled a proportion of people with bilateral surgery.

Twenty-eight of these 34 studies compared non-steroidal anti-inflammatory drugs (NSAIDs) plus steroids with steroids alone. Six studies compared NSAIDs (on their own or with placebo) with steroids. A variety of NSAIDs were used, including ketorolac, diclofenac, nepafenac, indomethacin, bromfenac and pranopfen. Follow-up ranged from one month to 12 months. The majority of studies (n = 23) followed up to two months or less. In general, the studies were poorly reported. We did not judge any of the studies at low risk of bias in all domains.

There was low-certainty evidence that people receiving topical NSAIDs in combination with steroids may have a lower risk of poor vision due to macular oedema (MO) at three months after cataract surgery compared with people receiving steroids alone (risk ratio (RR) 0.40, 95% confidence interval (CI) 0.27 to 0.61; eyes = 1360; studies = 5; I^2 = 5%). There were very little data for 12 months (only one study reported poor vision due to MO at this time point) and we judged this to have very low-certainty evidence. Similarly, we judged the evidence on 'clinically symptomatic MO' to be low-certainty. There was evidence on central retinal thickness at three months, but this was inconsistent (I^2 = 87%). Results ranged from -30.9 microns in favour of NSAIDs plus steroids to 7.44 microns in favour of steroids alone. Similarly, data on best corrected visual acuity (BCVA) were inconsistent. Nine out of 10 trials reporting this outcome found between-group differences of less than 0.1 logMAR.

None of the six studies comparing NSAIDs alone with steroids reported on poor vision due to MO at three months or 12 months. We judged the evidence on MO to be low-certainty. There was low-certainty evidence that mean central retinal thickness was lower in the NSAIDs group at three months (mean difference (MD) -22.64 microns, 95% CI -38.86 to -6.43; eyes = 121; studies = 2; I^2 = 0%). Two studies reported BCVA at three months, and the results of these trials were inconsistent, but both found differences of less than 0.1 logMAR between groups.

Quality of life was only reported in one of the 34 studies, and it was not fully reported other than to comment on lack of differences between groups. In general, no major adverse events were noted - the main consistent observation was burning or stinging.

Overall completeness and applicability of evidence

There were a relatively large number of trials, and these studies have a wide global range which means their results will be globally applicable.

The included studies compared NSAIDs and steroids in cataract surgery using phacoemulsification, extracapsular cataract extraction (ECCE) and intracapsular cataract extraction (ICCE) surgical techniques. However, the more recent trials exclusively used phacoemulsification, which may make their findings less applicable to parts of the world where resources are less available and ECCE is standard.

The aim of this review was to assess whether the use of NSAIDs had an impact on visual loss due to MO in the long-term. The evidence is very sparse with respect to that question, with only one study with high attrition, reporting on visual loss due to MO at 12 months after surgery. This is clearly an important gap in the evidence.

There are many trials looking at the short-term effects of NSAIDs, but there is considerable variation in terms of types, doses and regimens of NSAIDs and steroids used. One aspect that we have not highlighted in this review, but has been discussed elsewhere (Kim 2016a), is the potency of the steroid used in the comparison group. Use of low potency steroids, such as fluorometholone 0.1%, may lead to an overestimate of the relative effect of NSAIDs.

Certainty of the evidence

We graded the evidence as low- to very low-certainty. In general, the trials were poorly reported and it was difficult to judge the extent to which bias had been avoided. We did not judge any of the studies at low risk of bias for all domains. Many trials were not properly masked and, in a few studies, there were problems with attrition bias and selective outcome reporting. For outcomes that had more data we identified the possibility of publication bias with an asymmetric funnel plot. There were also problems with directness. For example, many studies reported "CMO" but were not clear whether or not this was 'clinically significant', or indeed what this meant in terms of whether it caused both symptoms and signs. And in many of the older studies this could not be verified by optical coherence tomography (OCT).

Potential biases in the review process

We have made several modifications to the original protocol (see Differences between protocol and review), but these were made before the data extraction and analysis phases of the review.

Agreements and disagreements with other studies or reviews

A recent systematic review and meta-analysis has been published (Wielders 2015). This review included 17 trials. The reason why they had fewer trials than the current review was because they only included studies of phacoemulsification cataract surgery and they excluded studies that did not report the incidence of cystoid macular oedema (CMO).

The review by Wielders 2015 reported effect measures in the same order of magnitude as that suggested by this review, but because they reported odds ratios (ORs), rather than risk ratios (RRs), these effect estimates are exaggerated (further away from null). The authors concluded that the odds of CMO were reduced in people who were given NSAIDs, but they did not incorporate a judgement on the overall certainty (or quality) of the evidence in their conclusions, even though they had assessed the risk of bias in the included trials using two different methods. It is also notable that, although the abstract highlights the fact that 17 trials were included in the review, it is less clearly pointed out that the effect estimates were based on a relatively small subset of these trials. This review was subsequently criticised because it did not fully incorporate an assessment of visual loss due to CMO, because the conclusions were based on so few trials, and because of the likely exclusion of studies that did not report any events (Kim 2016).

A report by the American Academy of Ophthalmology, also published in 2015, was more conservative in its conclusions (Kim 2015). This was a narrative review of the literature with no meta-analysis, nor any assessment of the quality of the evidence. They concluded that NSAIDs reduced the incidence of CMO, and may increase visual recovery, depending on the treatment of the comparator group, however, they concluded that the use of NSAIDs did not alter long-term (3 months) visual outcomes, a finding which is supported by the current review.

One slightly older systematic review published in 2014, included 15 trials and did include an overall GRADE assessment of the certainty of the evidence, which they judged to be low- to moderate-certainty for inflammation, low-certainty for visual acuity and high-certainty for CMO (Kessel 2014). This review again focused on phacoemulsification. It was restricted to the comparison of NSAIDs (on their own or with placebo) versus steroids alone. They cited the previously published protocol of this review justifying theirs as being different for these two reasons. They evaluated inflammation within one week of surgery and MO at any time point. There are some differences between the current review and Kessel 2014 in terms of the included studies. This is because the searches for the current review were restricted to evidence relating to MO. However, the trials contributing data to the analysis of MO are similar in the two reviews. Kessel 2014 included one study that we judged was probably not a randomised controlled trial (RCT) (Miyake 2000), and one study that we have included in the NSAIDs plus steroids comparison (Wang 2013). The estimates of effect for MO reported in Kessel 2014 and reported in this review are of a similar order of magnitude, although Kessel 2014 reports a stronger effect. This can be attributed to the fact that, when extracting data from studies using the Miyake 1977 classification, Kessel 2014 considered Grades 2 to 3 as MO, whereas in the current review we considered Grades 1 to 3. The main difference between the reviews is in the grading of the certainty of the evidence. Kessel 2014 considered the evidence to be high-certainty. It is not clearly stated why, but the footnote refers to a RR of 6, which we understand to mean that it is a strong effect, therefore they have not downgraded. We have considered the evidence on MO to be low-certainty, downgrading for risk of bias and publication bias (Summary of findings 2).

AUTHORS' CONCLUSIONS

Implications for practice

Using topical NSAIDs may reduce the risk of developing macular oedema after cataract surgery, although it is possible that current estimates as to the size of this reduction are exaggerated due to selective non-reporting of negative studies. It is unclear the extent to which this reduction has an impact on the visual function and quality of life of patients. There is little evidence to suggest any important effect on vision after surgery

The value of adding topical NSAIDs to steroids, or using them as an alternative to topical steroids with a view to reducing the risk of poor visual outcome after cataract surgery is uncertain. This is reflected in wide variations in modern practice. The role of the relative effectiveness and safety of NSAIDs as an alternative to steroids in the control of post operative inflammation is being addressed in another Cochrane Review (Gonzales 2013).

Implications for research

Future trials should address the remaining clinical uncertainty of whether prophylactic topical NSAIDs are of benefit, particularly with respect to longer-term follow-up (at least to 12 months), and should be large enough to detect to detect reduction in the risk of the outcome of most interest to patients, which is chronic macular oedema leading to visual loss. They should be rigorously conducted and double-masked.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Almeida 2008

Methods	**Study design:** Parallel group RCT **Open-label**
Participants	**Country:** Canada **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: NR (53) • *Number (%) of people followed up*: 38 (72%) eyes • *Average age in years*: 71 • *Age range in years*: 45-92 • *Percentage women*: 51% • *Ethnic group*: NR • *Percentage with diabetes*: 19% • *Percentage with uveitis*: 2% **Comparator: Steroids alone** • *Number of people (eyes) randomised*: NR (53) • *Number (%) of people followed up*: 42 (79%) eyes • *Average age in years*: 72 • *Age range in years*: 45-92 • *Percentage women*: 70% • *Ethnic group*: NR • *Percentage with diabetes*: 23% • *Percentage with uveitis*: 0% **Inclusion criteria:** Clinic patient having phacoemulsification with IOL implantation in their first eye; agreed to participate **Exclusion criteria:** Hypersensitivity to the NSAID drug class; aspirin/NSAID-induced asthma; pregnancy in the third trimester **Pretreatment:** More women in control group (70%) versus ketorolac group (51%), but unclear of importance of this difference **Eyes**: 106 eyes of 98 patients enrolled but clinical trials registry specifies first eye surgery only

Interventions	**Intervention: NSAIDs plus steroids**
	• ketorolac tromethamine 0.5% (Acular)
	  ○ *Times per day*: 4 times
	  ○ *Duration preoperative:* 2 days
	  ○ *Duration postoperative: 28 days*
	• prednisolone acetate 1% (brand name not reported)
	  ○ *Times per day*: 4 times a day for 7 days, twice a day for 7 days
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days*: 14
	Comparator: Steroids alone
	• prednisolone acetate 1% (brand name not reported)
	  ○ *Times per day*: 4 times a day for 7 days, twice a day for 7 days

Almeida 2008 (*Continued*)

	○ *Duration preoperative: days*: 0 ○ *Duration postoperative: days*: 14 All participants also received gatifloxacin 0.3% (Zymar) 4 times a day for 1 week **Type of surgery:** phacoemulsification
Outcomes	**Follow-up:** 1 month • Adverse effects • CMO (not defined but OCT used) • Change in total macular volume
Contact details	**Authors name:** Sherif El-Defrawy **Institution:** Queen's University, Ontario, Canada **Email:** eldefras@hdh.kari.net **Address:** Department of Ophthalmology, Queen's University, Hotel Dieu Hospital, Brock Wing 230A, 166 Brock Street, Kingston, Ontario K7L 5G2, Canada
Notes	**Funding sources:** "Funded by a Queen's University grant, Kingston, Ontario, Canada" **Declaration of interest:** "No author has a financial or proprietary interest in any material or method mentioned." **Date study conducted:** June 2006 to May 2007 (from clinical trials registry entry) **Trial registration number:** NCT00335439 **Contacting study investigators:** Not contacted

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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Judgement comment: Not reported how list was generated.
Allocation concealment (selection bias)	High risk	Quote: "open-label non-masked." Judgement comment: High risk of bias, given open-label nature of trial
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: Open-label study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: Open-label study.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "98 were assessed at 1 week and 80 at 1 month." Judgement comment: 38/53 (72%) in ketorolac group seen at 1 month versus 42/53 (79%) of non-treated group. One case of CMO excluded in non-treated group; 3 ketorolac-related AEs excluded

Almeida 2008 (*Continued*)

Selective reporting (reporting bias)	Low risk	Judgement comment: Only one outcome specified on clinical trials registry and this outcome was the main focus of the published report

Almeida 2012

Methods	**Study design:** Parallel group RCT
Participants	**Country:** Canada **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: NR • *Number (%) of people followed up*: 54 (NR but overall 84% follow-up) • *Average age in years*: NR (but overall average age was 72 years) • *Age range in years*: NR (but overall range was 50 to 88 years) • *Percentage women*: NR (but overall 54% were women) • *Ethnic group*: NR • *Percentage with diabetes*: NR (but "low risk" population) • *Percentage with uveitis*: NR (but "low risk" population) **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: NR • *Number (%) of people followed up*: 54 (NR but overall 84% follow-up) • *Average age in years*: NR (but overall average age was 72 years) • *Age range in years*: NR (but overall range was 50 to 88 years) • *Percentage women*: NR (but overall 54% were women) • *Ethnic group*: NR • *Percentage with diabetes*: NR (but "low risk" population) • *Percentage with uveitis*: NR (but "low risk" population) **Comparator: Steroids plus placebo** • *Number of people (eyes) randomised*: NR • *Number (%) of people followed up*: 54 (NR but overall 84% follow-up) • *Average age in years*: NR (but overall average age was 72 years) • *Age range in years*: NR (but overall range was 50 to 88 years) • *Percentage women*: NR (but overall 54% were women) • *Ethnic group*: NR • *Percentage with diabetes*: NR (but "low risk" population) • *Percentage with uveitis*: NR (but "low risk" population) **Inclusion criteria:** 18 years of age or older; cataract and were expected to have phacoemulsification with implantation of a posterior chamber IOL **Exclusion criteria:** Pre-existing retinal disease (e.g. diabetic retinopathy, vein occlusion, exudative macular degeneration); previous uveitis, previous intraocular surgery; allergy or hypersensitivity to NSAIDs. "Enrolled patients who had complicated cataract surgery (e.g. significant corneal edema, posterior capsule rupture, vitreous loss, dropped nuclear material, retained cortical material, or an IOL not placed in the capsular bag) were subsequently excluded." **Pretreatment:** "There were no differences in age, sex, or operative eye between the 3

	groups." **Eyes:** Probably one eye only included in the trial but not clearly reported and unclear how selected
Interventions	**Intervention 1: NSAIDs plus steroids** • ketorolac 0.5% (brand name not reported) ○ *Times per day*: 4 times ○ *Duration preoperative: days*: 1 ○ *Duration postoperative: days*: 28 • prednisolone 1% (brand name not reported) ○ *Times per day*: 4 times a day for 7 days, 3 times a day for 7 days, twice a day for 7 days, once a day for 7 days ○ *Duration preoperative: days*: 0 ○ *Duration postoperative: days*: 28 **Intervention 2: NSAIDs plus steroids** • nepafenac 0.1% (brand name not reported) ○ *Times per day*: 4 times ○ *Duration preoperative: days*: 1 ○ *Duration postoperative: days*: 28 • prednisolone 1% (brand name not reported) ○ *Times per day*: 4 times a day for 7 days, 3 times a day for 7 days, twice a day for 7 days, once a day for 7 days ○ *Duration preoperative: days*: 0 ○ *Duration postoperative: days*: 28 **Comparator: Steroids plus placebo** • sterile saline drops ○ *Times per day*: 4 times ○ *Duration preoperative: days*: 1 ○ *Duration postoperative: days*: 28 • prednisolone 1% (brand name not reported) ○ *Times per day*: 4 times a day for 7 days, 3 times a day for 7 days, twice a day for 7 days, once a day for 7 days ○ *Duration preoperative: days*: 0 ○ *Duration postoperative: days*: 28 All participants received gatifloxacin 0.3% drops 4 times a day starting 3 days before surgery and continued for 1 week after surgery **Type of surgery:** Phacoemulsification
Outcomes	**Follow-up:** 1 month • Quality of life (COMTOL questionnaire) • Change in CRT (not used in the analysis because no SD reported) • Change in BCVA logMAR • Change in total macular volume • Change in average macular cube thickness
Contact details	**Authors name:** David RP Almeida **Institution:** Queen's University, Ontario, Canada **Email:** dalmeida@evolation-medical.com **Address:** Department of Ophthalmology, Queen's University, Hotel Dieu Hospital, 166

Almeida 2012 (*Continued*)

	Brock Street, Eye Centre (Johnson 6), Kingston, Ontario K7L 5G2, Canada
Notes	**Funding sources:** "Funded by an unrestricted Queen's University educational research grant." **Declaration of interest:** "No author has a financial or proprietary interest in any material or method mentioned." **Date study conducted:** March 2010 to May 2011 **Trial registration number:** NCT01395069 **Contacting study investigators:** Trial authors not contacted.

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 receive a placebo (sterile saline drops), nepafenac 0.1%, or ketorolac 0.5%." Judgement comment: Not reported how list was generated.
Allocation concealment (selection bias)	Unclear risk	Quote: "The placebo, nepafenac, and ketorolac suspensions were supplied in identical generic drop bottles that were individually made by the Kingston General Hospital Investigational Pharmacy division. Bottles concealed medication information and were labelled with study identification number, patient identification number, expiration date, and emergency contact information only." Judgement comment: Unclear if investigators involved in the treatment allocation were masked
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The placebo, nepafenac, and ketorolac suspensions were supplied in identical generic drop bottles that were individually made by the Kingston General Hospital Investigational Pharmacy division. Bottles concealed medication information and were labelled with study identification number, patient identification number, expiration date, and emergency contact information only." Judgement comment: Placebo-controlled study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The placebo, nepafenac, and ketorolac suspensions were supplied in identical generic drop bottles that were individually made by the Kingston General Hospital Investigational Pharmacy division. Bottles concealed medication information and were labelled with study identification number, patient identification number, expiration date, and emergency contact information only."

Almeida 2012 (*Continued*)

		Judgement comment: Placebo-controlled study which probably means that the outcome assessors were masked
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "One hundred sixty-two patients, 54 in each arm, made up the intent-to-treat data set." Quote: "Ninety-seven patients (35 placebo, 32 ketorolac, 30 nepafenac) completed the COMTOL interview questionnaire (60.0% response rate)." Judgement comment: 84% follow-up. Not clearly reported but no evidence for any differential drop out by intervention group. 31 patients out of 193 lost to follow-up (16%). However, only 97 patients (60%) completed the COMTOL interview questionnaire and no further breakdown of losses to follow-up in each group provided
Selective reporting (reporting bias)	Unclear risk	Judgement comment: Outcomes on clinical trial registry entry (NCT01395069) were reported but the trial was retrospectively registered

Asano 2008

Methods	**Study design:** Parallel group RCT
Participants	**Country:** Japan **Setting:** 5 Eye hospitals **Intervention: NSAIDs alone** • *Number of people (eyes) randomised*: 75 (75) • *Number (%) of people followed up*: 71 (95%) • *Average age in years*: 66 • *Age range in years*: NR • *Percentage women*: 56% • *Ethnic group*: NR • *Percentage with diabetes*: 0 (excluded) • *Percentage with uveitis*: 0 (excluded) **Comparator: Steroids alone** • *Number of people (eyes) randomised*: 75 (75) • *Number (%) of people followed up*: 71 (95%) • *Average age in years*: 66 • *Age range in years*: NR • *Percentage women*: 55% • *Ethnic group*: NR • *Percentage with diabetes*: 0 (excluded) • *Percentage with uveitis*: 0 (excluded) **Inclusion criteria:** Age 55 to 75 years of age; nuclear hardness of Emery-Little grade IV or less; surgery in 1 eye only **Exclusion criteria:** Acute infection or inflammation within 1 month after initiation of

	the study; allergy to NSAIDs, steroids, or fluorescein; history of eye trauma or intraocular disease other than cataract; pseudoexfoliation syndrome; uveitis; glaucoma; diabetes and related complications; kidney disease;asthma or chronic airway disease; uncontrolled hypertension;severe heart failure; myocardial infarction or cerebrovascular disorders; intraoperative complications such as posterior capsule rupture, vitreous loss, retained lens nucleus, or lens fragments in the vitreous **Pretreatment:** None noted. Compared age, gender, duration of surgery, ultrasound time, irrigating solution and hardness of crystalline lens **Eyes:** One eye, unclear how selected.
Interventions	**Intervention: NSAIDs alone** • diclofenac sodium 0.1% (brand name not reported) ○ *Times per day*: 4 times on day of surgery; 3 times a day postoperative ○ *Duration preoperative: days*: 3 hours, 2 hours, 1 hour, and 30 minutes before surgery ○ *Duration* postoperative*: days*: 56 **Comparator: Steroids alone** • betamethasone sodium 0.1% (brand name not reported) ○ *Times per day*: 4 times on day of surgery; 3 times a day postoperative ○ *Duration preoperative: days*: 3 hours, 2 hours, 1 hour, and 30 minutes before surgery ○ *Duration postoperative: days*: 56 Concomitant mydriatic and antibiotic agents were permitted. **Type of surgery:** Phacoemulsification
Outcomes	**Follow-up:** 8 weeks • Adverse effects • CMO reported at 5 weeks only (fluorescein angiography using Miyake 1977 classification, grades I-III taken as CMO) • Laser flare-cell photometry (mean value of anterior chamber flare reported) • BCVA logMAR (final value)
Contact details	**Authors name:** Kensaku Miyake **Institution:** Shohzankai Medical Foundation, Miyake Eye Hospital **Email:** miyake@spice.or.jp **Address:** Shohzankai Medical Foundation, Miyake Eye Hospital, 3-15-68, Ozone, Kita-ku, Nagoya, 462-0825, Japan
Notes	**Funding sources:** NR **Declaration of interest:** "No author has a financial or proprietary interest in any material or method mentioned." **Date study conducted:** April 2004 to September 2005 **Trial registration number**: NR **Contacting study investigators:** Trial authors not contacted.

Risk of bias			***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**	

Random sequence generation (selection bias)	Unclear risk	Quote: "The test drugs were assigned to patients at random after the controller validated that the assigned therapy was indistinguishable from the alternative therapy." Judgement comment: Not reported how list was generated.
Allocation concealment (selection bias)	Low risk	Quote: "The controller kept the assignment code until completion of the study." Judgement comment: This probably means that the allocation was concealed from the investigators although it was not clearly reported who the controller was exactly
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The test drugs were assigned to patients at random after the controller validated that the assigned therapy was indistinguishable from the alternative therapy. The controller kept the assignment code until completion of the study. The controller created an emergency code, which was given to the principal investigator in an envelope. The investigator could open the envelope if severe adverse effects developed. The test drugs were administered to each patient 3 hours, 2 hours, 1 hour, and 30 minutes before surgery and 3 times a day for 8 weeks after surgery." Judgement comment: Although not clearly stated that participants and personnel were unaware of which treatment received, the study was placebo-controlled and efforts made to keep the allocation away from investigators so we assume that masking was done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The test drugs were assigned to patients at random after the controller validated that the assigned therapy was indistinguishable from the alternative therapy. The controller kept the assignment code until completion of the study. The controller created an emergency code, which was given to the principal investigator in an envelope. The investigator could open the envelope if severe adverse effects developed. The test drugs were administered to each patient 3 hours, 2 hours, 1 hour, and 30 minutes before surgery and 3 times a day for 8 weeks after surgery." Judgement comment: Although not clearly stated that outcome assessors were unaware of which treatment received, the study was placebo-con-

Asano 2008 (*Continued*)

		trolled and efforts made to keep the allocation away from investigators so we assume that masking was done
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Of the 150 eyes initially included in this study, 75 were assigned to the diclofenac group and 75 to the betamethasone group. Four patients in each group dropped out of the study: 1 in each group due to complications; 3 in the diclofenac group and 2 in the betamethasone group due to a discontinuation proposal (there were patients who withdrew their consent during the course of this study); 1 in the betamethasone group for not returning to the hospital 2 weeks after surgery. Seventy-one eyes in each group completed the study. " Judgement comment: In the results text quoted follow-up appeared to be high (95%) and equal between groups but in table 3 visual acuity results follow-up was lower 58/75 (77%) versus 52/75 (69%) and unclear why Judgement comment: Some of the exclusion criteria may have lead to bias if they occurred differently between two treatment groups: "acute infection or inflammation within 1 month after initiation of the study" and "intraoperative complications such as posterior capsule rupture, vitreous loss, retained lens nucleus, or lens fragments in the vitreous", however these exclusions were not reported
Selective reporting (reporting bias)	High risk	Judgement comment: No access to protocol or trials registry entry but noted that data on CMO were reported only at 5 weeks, but other data available at 8 weeks follow-up

Brown 1996

Methods	**Study design:** Parallel group RCT
Participants	**Country:** USA **Setting:** Eye hospital **Intervention group: NSAIDs alone** • *Number of people (eyes) randomised*: NR • *Number (%) of people followed up*: NR • *Average age in years*: NR • *Age range in years*: NR • *Percentage women*: NR • *Ethnic group*: NR • *Percentage with diabetes*: NR (but people with DR excluded)

	• *Percentage with uveitis*: 0 (people with uveitis excluded) **Comparator: Steroids alone** • *Number of people (eyes) randomised*: NR • *Number (%) of people followed up*: NR • *Average age in years*: NR • *Age range in years*: NR • *Percentage women*: NR • *Ethnic group*: NR • *Percentage with diabetes*: NR (but people with DR excluded) • *Percentage with uveitis*: 0 (people with uveitis excluded) **Inclusion criteria:** Undergoing phacoemulsification with posterior capsular opacification after lens (PCOL) implantation **Exclusion criteria:** History of systemic or ocular inflammation (iritis, uveitis); taking oral or ophthalmic steroids or NSAIDs; other ocular disease such as glaucoma, corneal disease, or diabetic retinopathy **Pretreatment:** Group differences not reported. **Eyes:** Unclear if one or both eyes included.
Interventions	**Intervention group: NSAIDs alone** • diclofenac sodium 0.1% (Voltaren Ophthalmic, Ciba Vision Ophthalmics Duluth, Ga) ○ *Times per day*: 4 times a day for 7 days; twice a day for 21 days ○ *Duration preoperative: days*: 0 ○ *Duration postoperative: days*: 28 **Comparator: Steroids alone** • prednisolone acetate 1% (Pred Forte, Allergan) ○ *Times per day*: 4 times a day for 7 days; twice a day for 21 days ○ *Duration preoperative: days*: 0 ○ *Duration postoperative: days*: 28 All patients had gentamicin drops for 7 days postoperative. **Type of surgery:** Phacoemulsification
Outcomes	**Follow-up:** 1 month • Laser flare-cell photometry (mean value of anterior chamber flare reported, photons) but was not possible to calculate SD so not used in the analysis.
Contact details	**Authors name:** Rose Marie Brown **Institution:** New York Hospital - Cornell Medical Center **Email:** NR **Address:** Cornell University Medical College, 520 E. 70th St, Starr 817, New York, NY 10021
Notes	**Funding sources:** "Supported in part from a grant from Ciba Vision Ophthalmics, Duluth, Ga." **Declaration of interest**: NR **Date study conducted:** 1991 **Trial registration number:** NR **Contacting study investigators:** Trial authors not contacted.

Brown 1996 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote "We conducted a prospective, randomised study." "The patients were randomly assigned to receive..." Judgement comment: Not reported how list was generated. Study was described as "randomised" but with no further details
Allocation concealment (selection bias)	Unclear risk	Judgement comment: Not reported how allocation administered. Study was described as "randomised" but with no further details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: No information on masking. We assume that in absence of reporting on this, patients and personnel were not masked
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Judgement comment: For measurement of inflammation - Quote: "Neither examiner knew which of the study groups the patient was enrolled in." But for other outcomes, masking not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: Follow-up not reported. Unclear how many people seen at 1 month
Selective reporting (reporting bias)	Unclear risk	Judgement comment: No access to protocol or trials registry entry

Cervantes-Coste 2009

Methods	**Study design:** Parallel group RCT
Participants	**Country:** Mexico **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: 30 (30) • *Number (%) of people followed up*: 30 (100%) • *Average age in years*: 73 • *Age range in years*: 52 to 88 • *Percentage women*: 67% • *Ethnic group*: NR • *Percentage with diabetes*: 17% • *Percentage with uveitis*: 0 (excluded) **Comparator: Steroids alone** • *Number of people (eyes) randomised*: 30 (30) • *Number (%) of people followed up*: 30 (100%)

	• *Average age in years*: 71 • *Age range in years*: 51 to 85 • *Percentage women*: 60% • *Ethnic group*: NR • *Percentage with diabetes*: 23% • *Percentage with uveitis*: 0 (excluded) **Inclusion criteria:** Adult patients 40 years of age or older; diagnosed with senile and/or metabolic cataract (according to the Lens Opacities Classification System LOCS III, with classification NO and NC 2-3); scheduled for surgery by phacoemulsification and IOL implantation inside the capsular bag; normal fundoscopy exam (if observance was possible) **Exclusion criteria:** Pregnancy or breastfeeding; history of ocular inflammatory or infectious eye disease; treatment for eye infection within 30 days prior to inclusion in the study;alterations on the eye surface (including dry eye); history of ocular surgery and/or trauma; knowledge or suspicion of allergy or hypersensitivity to the preservatives, steroids, topical NSAIDs, or any other component of the study medication; use of eye medications, including prostaglandin analogues; use of topical or systemic steroids within 30 days prior to inclusion in the study; use of topical or systemic NSAIDs within 14 days prior to inclusion in the study; non-controlled diabetes mellitus, based on clinical history and blood glucose level (126 mg); proliferative diabetic retinopathy, and/or macular oedema; preoperative mydriasis less than 6 mm prior to the study; synechiae; ocular alteration preventing adequate mydriasis such as iris atrophy; macular alteration documented by OCT, including macular oedema of any etiology, macular holes, epiretinal membrane, macular degeneration related to age, and central serous chorioretinopathy; the use of contact lens in the eye involved during the study **Pretreatment:** No differences noted; compared age, gender, operated eye, ocular and systemic pathology **Eyes:** One eye, unclear how selected.

Interventions	**Intervention: NSAIDs plus steroids**
	• nepafenac 0.1% (brand name not reported)
	  ○ *Times per day*: 1 drop every 15 minutes (4 doses) 1 hour prior to surgery; 3 times a day otherwise
	  ○ *Duration preoperative: days*: 1
	  ○ *Duration postoperative: days*: 42
	• dexamethasone (combined with tobramycin) (brand name not reported)
	  ○ *Times per day*: 4 times
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days*: 10
	Comparator: Steroids alone
	• dexamethasone (combined with tobramycin) (brand name not reported)
	  ○ *Times per day*: 4 times
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days*: 10
	Type of surgery: Phacoemulsification

Outcomes	**Follow-up:** 6 weeks • Poor vision outcome due to MO ("None of the patients developed clinically significant macular oedema associated with vision loss")

	• CRT at follow-up (final value) • Adverse effects • Inflammation ("inflammatory cells greater than 1+ during first week of postoperative visits") • Total macular volume Subgroup analysis by diabetes reported.
Contact details	**Authors name:** Guadalupe Cervantes-Coste **Institution:** Asociación Para Evitar la Ceguera en México I.A.P. Hospital **Email:** gpecervantes@hotmail.com **Address:** Av. México 85-5, México City, 06100 México
Notes	**Funding sources:** NR **Declaration of interest:** The authors have no conflicts of interest to disclose. **Date study conducted:** NR **Trial registration number:** NR **Contacting study investigators:** Trial authors not contacted.

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "This was a prospective, randomised, single-masked, single-center, longitudinal, experimental and comparative study in patients undergoing phacoemulsication cataract surgery." Judgement comment: Not reported how list was generated. Trial described as "randomised" but with no further details
Allocation concealment (selection bias)	Unclear risk	Judgement comment: Not reported how allocation administered.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The identity of patients receiving preoperative mydriatic or preoperative mydriatic and nepafenac was concealed from the surgeons." Judgement comment: Only the surgeons appeared to be masked.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement Comment: The study compared nepafenac versus no treatment so is essentially open-label. No information was provided on masking. We assume that in absence of reporting on this outcome, assessors were not masked
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All patients completed the follow-up visits over a 6-week period." Judgement comment: No patients appeared to have been excluded or lost to follow-up

Cervantes-Coste 2009 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Judgement comment: No access to protocol or trial registry entry

Chatziralli 2011

Methods	**Study design:** Parallel group RCT
Participants	**Country:** Greece **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: 73 (NR) • *Number (%) of people followed up*: 70 (96%) • *Average age in years*: 74 • *Age range in years*: NR • *Percentage women*: 39% • *Ethnic group*: NR • *Percentage with diabetes*: 9% • *Percentage with uveitis*: 0 (excluded) **Comparator: Steroids alone** • *Number of people (eyes) randomised*: 72 (NR) • *Number (%) of people followed up*: 68 (94%) • *Average age in years*: 74 • *Age range in years*: NR • *Percentage women*: 41% • *Ethnic group*: NR • *Percentage with diabetes*: 10% • *Percentage with uveitis*: 0 (excluded) **Inclusion criteria:** NR **Exclusion criteria:** History of intraocular surgery on the eye to be operated; any previous episode of uveitis in the eye to be operated; severe systemic disease (heart failure of the New York Heart Association stage III of IV, endstage renal failure, pulmonary failure, receiving chemotherapy); regular, systemic use of steroid or NSAIDs during the last 3 months **Pretreatment:** None noted; compared age, gender, baseline visual acuity, education, marital status, smoking, and various systemic ocular factors **Eyes:** Probably one eye only included in the trial but not clearly reported and unclear how selected

Interventions	**Intervention: NSAIDs plus steroids**
	• ketorolac tromethamine 0.5% (Acular, Allergan)
	  ○ *Times per day*: 3 times
	  ○ *Duration preoperative: days*: 3
	  ○ *Duration postoperative: days*: 28
	• dexamethasone 0.1% (in combination with tobramycin 0.3%) (Tobradex, Alcon)
	  ○ *Times per day*: 5 times a day preoperative, 4 times a day postoperative
	  ○ *Duration preoperative: days*: 3
	  ○ *Duration postoperative: days*: 28
	Comparator: Steroids alone

	• dexamethasone 0.1% (in combination with tobramycin 0.3%) (Tobradex, Alcon) ○ T*imes per day*: 5 times a day preoperative, 4 times a day postoperative ○ *Duration preoperative: days*: 3 ○ *Duration postoperative: days*: 28 **Type of surgery:** phacoemulsification
Outcomes	**Follow-up:** 6 weeks • Poor vision outcome due to MO • Adverse effects, pain and ocular discomfort (itching or foreign-body sensation) on a 0-10 visual analogue scale CMO (fundoscopy plus Amsler grid) • Inflammation (presence of corneal oedema, Tyndall reaction or conjunctival hyperemia) • BCVA logMAR (final value)
Contact details	**Authors name:** Irini Chatziralli **Institution:** Department of Ophthalmology, Veroia General Hospital **Email:** eirchat@yahoo.gr **Address:** Department of Ophthalmology, Veroia General Hospital, 28, Papanastasiou Street, GR-17342 Athens (Greece)
Notes	**Funding sources:** NR **Declaration of interest:** NR **Date study conducted:** October 2009 to January 2010 **Trial registration number:** NR **Contacting study investigators:** Trial authors not contacted.

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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomised to 1 of the 2 postoperative treatment arms." Judgement comment: Not reported how list was generated.
Allocation concealment (selection bias)	Unclear risk	Judgement comment: Not reported how allocation administered.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The study was masked to the patients, i.e. they received unmarked bottles so as to be unaware of which treatment they received."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: No information on masking of outcome assessors. We assume that in absence of reporting on this outcome, assessors were not masked

Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: Follow-up high and reasonably equal between groups: 70/73 (96%) in NSAIDs group versus 68/72 (94%) in steroid group
Selective reporting (reporting bias)	Unclear risk	Judgement comment: No access to protocol or trial registry entry

Donnenfeld 2006

Methods	**Study design:** Parallel group RCT
Participants	**Country:** USA **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: 25 (NR) • *Number (%) of people followed up*: NR • *Average age in years*: NR (age overall was 73 years) • *Age range in years*: NR • *Percentage women*: NR (overall 55% women) • *Ethnic group*: NR • *Percentage with diabetes*: 0 (excluded) • *Percentage with uveitis*: 0 (excluded) **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: 25 (NR) • *Number (%) of people followed up*: NR • *Average age in years*: NR (age overall was 73 years) • *Age range in years*: NR • *Percentage women*: NR (overall 55% women) • *Ethnic group*: NR • *Percentage with diabetes*: 0 (excluded) • *Percentage with uveitis*: 0 (excluded) **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: 25 (NR) • *Number (%) of people followed up*: NR • *Average age in years*: NR (age overall was 73 years) • *Age range in years*: NR • *Percentage women*: NR (overall 55% women) • *Ethnic group*: NR • *Percentage with diabetes*: 0 (excluded) • *Percentage with uveitis*: 0 (excluded) **Comparator: Steroids plus placebo** • *Number of people (eyes) randomised*: 25 (NR) • *Number (%) of people followed up*: NR • *Average age in years*: NR (age overall was 73 years) • *Age range in years*: NR • *Percentage women*: NR (overall 55% women)

	• *Ethnic group*: NR • *Percentage with diabetes*: 0 (excluded) • *Percentage with uveitis*: 0 (excluded) **Inclusion criteria:** Scheduled for phacoemulsification. **Exclusion criteria:** Known sensitivity to any ingredient in the study medications; monocular status; a history of previous intraocular surgery;diabetes mellitus; a history of uveitis, iritis, or intraocular inflammation; use of a systemic NSAID during the study or the week before surgery; or pupils that did not dilate to more than 5.0 mm before surgery or requiring mechanical pupil stretching; pregnant, nursing an infant, or planning a pregnancy **Pretreatment:** "There were no significant between-group differences in any demographic variable or baseline value." **Eyes**: Unclear if one or both eyes included.
Interventions	**Intervention: NSAIDs plus steroids** • ketorolac tromethamine 0.4% (brand name not reported) ◦ *Times per day*: 4 times a day for 3 days preoperative; 3 times every 15 minutes before surgery; 4 times a day for 21 days postoperative ◦ *Duration preoperative: days*: 3 ◦ *Duration postoperative: days*: 21 • prednisolone acetate 1% (brand name not reported) ◦ *Times per day*: 4 times a day for 14 days; twice a day for 7 days ◦ *Duration preoperative: days*: 0 ◦ *Duration postoperative: days*: 21 **Intervention: NSAIDs plus steroids** • ketorolac tromethamine 0.4% (brand name not reported) ◦ *Times per day*: 4 times a day for 1 day preoperative; every 15 mins in hour before surgery; 4 times a day for 21 days postoperative ◦ *Duration preoperative: days*: 1 ◦ *Duration postoperative: days*: 21 • prednisolone acetate 1% (brand name not reported) ◦ *Times per day*: 4 times a day for 14 days; twice a day for 7 days ◦ *Duration preoperative: days*: 0 ◦ *Duration postoperative: days*: 21 **Intervention: NSAIDs plus steroids** • ketorolac tromethamine 0.4% (brand name not reported) ◦ *Times per day*: every 15 mins in hour before surgery; 4 times a day for 21 days postoperative ◦ *Duration preoperative: days*: 0 ◦ *Duration postoperative: days*: 21 • prednisolone acetate 1% (brand name not reported) ◦ *Times per day*: 4 times a day for 14 days; twice a day for 7 days ◦ *Duration preoperative: days*: 0 ◦ *Duration postoperative: days*: 21 **Comparator: Steroids plus placebo** • prednisolone acetate 1% (brand name not reported) ◦ *Times per day*: 4 times a day for 14 days; twice a day for 7 days ◦ *Duration preoperative: days*: 0 ◦ *Duration postoperative: days*: 21

Donnenfeld 2006 (*Continued*)

	• placebo (vehicle) ○ *Times per day*: every 15 mins in the hour before surgery. 4 times a day postoperatively ○ *Duration preoperative: days*: 0 ○ *Duration postoperative: days*: 21 All participants received topical gatifloxacin 0.3% 4 times a day for 3 days before cataract surgery and for 1 week after surgery **Type of surgery:** Phacoemulsification
Outcomes	**Follow-up:** 3 months • Adverse effects (patient discomfort on a 1 to 5 scale and need for analgesia) • CMO (at 2 weeks only, "clinically significant CME" but otherwise not defined, no OCT) • Inflammation ("Mean inflammation score" but was not possible to calculate SD) • BCVA logMAR (final value)
Contact details	**Authors name:** Eric D. Donnenfeld **Institution:** Ophthalmic Consultants of Long Island **Email:** eddoph@aol.com **Address:** Ophthalmic Consultants of Long Island, Ryan Medical Arts Building, 2000 North Village Avenue, Suite 402, Rockville Centre, New York 11570, USA
Notes	**Funding sources:** "Supported in part by an unrestricted grant from Allergan Inc., Irvine, California, and the Lions Eye Bank for Long Island, Long Island, New York, USA" **Declaration of interest:** "Drs. Donnenfeld, Perry, and Wittpenn are consultants to Allergan Pharmaceuticals. No other author has a financial or proprietary interest in any material or method mentioned." **Date study conducted:** NR **Trial registration number:** NR **Contacting study investigators:** Trial authors not contacted.

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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Group assignment was based on a random-number-generated protocol that was created before initiation of the study."
Allocation concealment (selection bias)	Unclear risk	Judgement comment: Not reported how allocation administered.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Judgement comment: Placebo-controlled, but not clear if masking was successful - some of the groups had different schedules
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Judgement comment: Placebo-controlled but not clear if masking was successful - some of the groups had different schedules. Corneal endothelial cell

Donnenfeld 2006 (*Continued*)

		counts and OCT scans were evaluated by masked specialists. It was unclear whether assessors of other outcomes were aware of the treatment allocation, or if only the specialists were affected
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: Follow-up not reported.
Selective reporting (reporting bias)	Unclear risk	Judgement comment: No access to protocol or trial registry entry

Elsawy 2013

Methods	**Study design:** Parallel group RCT
Participants	**Country:** Egypt **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: 35 (43) • *Number (%) of people followed up*: NR • *Average age in years*: NR • *Age range in years*: NR • *Percentage women*: 34% • *Ethnic group*: NR • *Percentage with diabetes*: 100% • *Percentage with uveitis*: NR **Comparator: Steroids alone** • *Number of people (eyes) randomised*: 35 (43) • *Number (%) of people followed up*: NR • *Average age in years*: NR • *Age range in years*: NR • *Percentage women*: 40% • *Ethnic group*: NR • *Percentage with diabetes*: 100% • *Percentage with uveitis*: NR Some inconsistencies in the data. Not clearly stated exactly number of people (eyes) randomly allocated to each group and followed up **Inclusion criteria:** High risk characteristics for the postoperative development of CME, one of the risk factors for CME (beside diabetic retinopathy). History of retinal vein occlusion or presence of epiretinal membrane or preoperative use of prostaglandin analogues eye drops **Exclusion criteria:** NR **Pretreatment:** Compared age, gender, type of diabetes, duration of diabetes, retinal vein occlusion, epiretinal membrane and prostaglandin drops. Some imbalances, e.g. more prostaglandin eye drop use in control group **Eyes:** 86 eyes of 70 people. **Type of surgery:** Phacoemulsification

Elsawy 2013 (*Continued*)

Interventions	**Intervention: NSAIDs plus steroids**
	• ketorolac tromethamine 0.4% (brand name not reported)
	  ○ *Times per day*: twice a day
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days*: 84
	• dexamethasone 0.1% (brand name not reported)
	  ○ *Times per day*: 4 times
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days*: 84
	Comparator: Steroids alone
	• dexamethasone 0.1% (brand name not reported)
	  ○ *Times per day*: 4 times
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days*: 84
	Type of surgery: Phacoemulsification

Outcomes	**Follow-up:** 12 weeks • CMO (clinical examination, unclear if OCT-verified)
Contact details	**Authors name:** Moataz F Elsawy **Institution:** Menoufia University Hospital **Email:** mfelsawy@yahoo.co.uk **Address:** Ophthalmology Department, Menoufia University Hospital, Menoufia, 53211, Egypt
Notes	**Funding sources:** NR **Declaration of interest:** "The authors report no conflicts of interest in this work." **Date study conducted:** January 2011 to March 2012 **Trial registration number:** NR **Contacting study investigators:** Trial authors not contacted.

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The randomisation process used four opaque envelopes in two containers. The first container had (1) for dexamethasone drops only, and (2) for combined drops, and the second container had the name of patients listed for cataract surgery on that day. Patients were randomised to one of the regimes by asking an independent person to choose one envelope from each container." Judgement comment: Unusual random allocation process.
Allocation concealment (selection bias)	Unclear risk	Quote: "The randomisation process used four opaque envelopes in two containers. The first con-

		tainer had (1) for dexamethasone drops only, and (2) for combined drops, and the second container had the name of patients listed for cataract surgery on that day. Patients were randomised to one of the regimes by asking an independent person to choose one envelope from each container. All patients underwent phacoemulsification (divide and conquer)." Judgement comment: Unusual allocation process.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: No information on masking. We assume that in absence of reporting on this, patients and personnel were not masked
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: No information on masking. We assume that in absence of reporting on this, outcome assessors were not masked
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: Follow-up not reported.
Selective reporting (reporting bias)	Unclear risk	Judgement comment: No access to protocol or trial registry entry

Endo 2010

Methods	**Study design:** Parallel group RCT **Open-label**
Participants	**Country:** Japan **Setting:** Eye hospital **Intervention: NSAIDs alone** • *Number of people (eyes) randomised*: 40 (40) • *Number (%) of people followed up*: 31 (78%) • *Average age in years*: 68 • *Age range in years*: NR (overall age range 37-84 years) • *Percentage women*: 48% • *Ethnic group*: NR • *Percentage with diabetes*: 100% • *Percentage with uveitis*: 0 (excluded) **Comparator: Steroids alone** • *Number of people (eyes) randomised*: 35 (35) • *Number (%) of people followed up*: 31 (89%) • *Average age in years*: 69 • *Age range in years*: NR • *Percentage women*: 42% • *Ethnic group*: NR • *Percentage with diabetes*: 100%

	• *Percentage with uveitis*: 0 (excluded) **Inclusion criteria:** Patients with diabetes undergoing small incision phacoemulsification with IOL implantation **Exclusion criteria:** foveal thickness of 250 microns or more; severe diabetic retinopathy for which ocular surgery (including photocoagulation) indicated;use of topical medications for glaucoma, uveitis and other diseases that cause CMO; ocular allergies to bromfenac or steroids (steroid group); use of systemic steroids or NSAIDs; serious cardiac, cerebral or renal disease **Pretreatment:** No major imbalances; compared age, gender, hypertension, blood urea nitrogen. HbA1c slightly higher in NSAIDs group **Eyes:** One eye, unclear how selected.
Interventions	**Intervention: NSAIDs alone** • bromfenac sodium (Bronuck, Senju,Pharmaceutical Company Ltd, Osaka,Japan) ○ T*imes per day*: twice a day ○ *Duration preoperative: days*: 0 ○ *Duration postoperative: days*: 42 **Comparator: Steroids alone** • betamethasone sodium phosphate (with fradiomycin sulfate) followed by fluorometholone 0.1%(Rinderon-A, Shionogi, Osaka, Japan and Flumetholon 0.1%, Santen) ○ *Times per day*: 4 times a day for 7 days (betamethasone); 4 times a day for 35 days (fluorometholone) ○ *Duration preoperative: days*: 0 ○ *Duration postoperative: days*: 42 Preoperatively, all participants received gatifloxacin (four times daily for 1 day preoperatively; on the day of surgery, they received 0.5% tropicamide, 0.5% phenylephrine hydrochloride every 30 mins 2 hours preoperatively. Postoperatively, gatifloxacin four times daily until week 6, and 0.5% tropicamide and 0.5% phenylephrine hydrochloride once daily for 1 week **Type of surgery:** Phacoemulsification
Outcomes	**Follow-up:** 6 weeks • CRT at follow-up (final value) • Adverse effects • Inflammation (anterior chamber flare values, photon count per millisecond) • BCVA logMAR (final value)
Contact details	**Authors name:** Naoko Endo **Institution:** Tokyo Women's Medical University Diabetes Centre **Email:** 51026745@mail.goo.ne.jp **Address:** Tokyo Women's Medical University Diabetes Centre, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-0054, Japan
Notes	**Funding sources:** NR **Declaration of interest:** "The authors have no financial interest in any aspect of this article." **Date study conducted:** March 2005 to May 2007 **Trial registration number:** NR

Endo 2010 (*Continued*)

	Contacting study investigators: Trial authors not contacted.

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "A prospective open-label trial was conducted using the envelope method." Judgement comment: Not reported how list was generated.
Allocation concealment (selection bias)	Unclear risk	Judgement comment: Although mentioned "envelope method", not enough information on how the allocation was administered
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: Open-label study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: Open-label study.
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: 17% (13/75) of patients were excluded. Vague reasons were provided. Three were excluded because of difficulty with the OCT measurement. Ten people (10 eyes) dropped out of the study for the following reasons: poor health (8) , posterior capsular rupture (1) and epidemic keratoconjunctivitis (1). No details were provided about the 'difficulties with OCT measurements' and 'poor health'. 31/40 (78%) in NSAIDs group and 31/35 (89%) in steroids group were followed-up but reasons for dropout by group were not clearly reported
Selective reporting (reporting bias)	Unclear risk	Judgement comment: No access to protocol or trial registry entry

Italian Diclofenac Study Group 1997

Methods	**Study design:** Parallel group RCT
Participants	**Country:** Italy **Setting:** Eye hospital **Intervention: NSAIDs alone** • *Number of people (eyes) randomised*: 141 (141) • *Number (%) of people followed up*: 118 (84%) • *Average age in years*: 68 • *Age range in years*: NR • *Percentage women*: 51% • *Ethnic group*: NR • *Percentage with diabetes*: NR • *Percentage with uveitis*: NR **Comparator: Steroids plus placebo** • *Number of people (eyes) randomised*: 140 (140) • *Number (%) of people followed up*: 111 (79%) • *Average age in years*: 68 • *Age range in years*: NR • *Percentage women*: 53% • *Ethnic group*: NR • *Percentage with diabetes*: NR • *Percentage with uveitis*: NR **Inclusion criteria:** 45 to 75 years of age; age-related cataract. **Exclusion criteria:** Ocular malformations; dry-eye syndrome (Schirmer I < 5 mm); glaucoma or ocular hypertension (IOP > 22 mmHg); vitreoretinal pathology; surgical complications (posterior capsule rupture, Descemet's membrane detachment, vitreous loss, significant intraocular haemorrhage, IOL dislocation); severe systemic affections; ocular surgery in the previous 2 months or had had bilateral surgery; hypersensitive to one or more of the study compounds; pregnant or nursing woman **Pretreatment:** No major imbalances in age, sex, IOP and operated eye. **Eyes:** One eye, unclear how selected.
Interventions	**Intervention: NSAIDs alone** • diclofenac 0.1% (Voltaren Ophthalmic) ◦ *Times per day*: 5 drops in 3 hours before surgery; 5 times a day on days 1 to 5; 3 times a day on days 6 to 140 ◦ *Duration preoperative: days*: 0 ◦ *Duration postoperative: days*: 140 **Comparator: Steroids plus placebo** • dexamethasone 0.1% (brand name not reported) ◦ *Times per day*: 5 times ◦ *Duration preoperative: days*: 0 ◦ *Duration postoperative: days*: 5 • placebo (not specified) ◦ *Times per day*: 5 drops in 3 hours before surgery; 3 times a day days 6 to 140 ◦ *Duration preoperative: days*: 0 ◦ *Duration postoperative: days*: 140 **Type of surgery:** ECCE

Italian Diclofenac Study Group 1997 (*Continued*)

Outcomes	**Follow-up:** 140 days • Adverse effects • CMO ("angiographic CME" using Miyake 1977)
Contact details	**Authors name:** Lucio Lobefalo **Institution:** NR **Email:** NR **Address:** via Gran Sasso 100, 1-66100 Chieti, Italy
Notes	**Funding sources:** NR **Declaration of interest:** "S. Bianco, MD, is a Ciba Vision Ophthalmics officer. None of the other authors has a proprietary or financial interest in diclofenac." **Date study conducted:** October 1992 to February 1994 **Trial registration number:** NR **Contacting study investigators:** Trial authors not contacted.

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: Not reported how list was generated. Trial was described as "randomised" but with no further details
Allocation concealment (selection bias)	Unclear risk	Judgement comment: Not reported how allocation administered. Trial was described as "randomised" but with no further details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Judgement comment: Placebo-controlled but masking of participants not described specifically
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "In each center, all patients were observed by the same examiner; surgeons and examiners were masked at all postoperative visits."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: Follow-up: 118/140 (84%) in diclofenac group and 111/141 (79%) in dexamethasone group followed up. Follow-up reasonably high and not very different between the two groups
Selective reporting (reporting bias)	Unclear risk	Judgement comment: No access to protocol or trials registry entry

Jung 2015

Methods	**Study design:** Parallel group RCT
Participants	**Country:** South Korea **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: 28 (28) • *Number (%) of people followed up*: NR • *Average age in years*: 67 • *Age range in years*: NR • *Percentage women*: 54% • *Ethnic group*: NR • *Percentage with diabetes*: 25% • P*ercentage with uveitis*: NR **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: 32 (32) • *Number (%) of people followed up*: NR • *Average age in years*: 68 • *Age range in years*: NR • *Percentage women*: 53% • *Ethnic group*: NR • *Percentage with diabetes*: 28% • P*ercentage with uveitis*: NR **Comparator: Steroids** • *Number of people (eyes) randomised*: 31 (31) • *Number (%) of people followed up*: NR • *Average age in years*: 67 • *Age range in years*: NR • *Percentage women*: 58% • *Ethnic group*: NR • *Percentage with diabetes*: 26% • *Percentage with uveitis*: NR **Inclusion criteria:** Males or non-pregnant females aged between 20- to 80-years-old **Exclusion criteria:** Poor general condition, including high blood pressure, poor blood glucose control, or renal failure; history of ocular trauma or disease; history of intraocular surgery; systemic or topical NSAIDs or corticosteroids use within 4 weeks of enrolment; known hypersensitivity to salicylates or other NSAIDs; and use of alpha-1 adrenergic antagonist or other analogous systemic medications that may increase the tendency for miosis during the operation (intraoperative floppy iris syndrome) **Pretreatment:** No major imbalances, age, sex, hypertension, diabetes, macular thickness and volume and ocular surface status compared **Eyes:** One eye, unclear how selected.
Interventions	**Intervention: NSAIDs plus steroids** • bromfenac sodium 0.1% (Bronuck, Senju Pharmaceutical co Ltd, Osaka, Japan) ◦ *Times per day*: twice a day plus 2 drops at 20-min intervals 2 hrs before surgery ◦ *Duration preoperative: days*: 3 ◦ *Duration postoperative: days*: 28 • prednisolone acetate 1% (brand name not reported)

	○ *Times per day*: 4 times ○ *Duration preoperative: days*: 0 ○ *Duration postoperative: days*: 28 **Intervention: NSAIDs plus steroids** • ketorolac 0.45% (Acuvail, Allergan Inc, CA, USA) ○ *Times per day*: twice a day plus 2 drops at 20-min intervals 2 hrs before surgery ○ *Duration preoperative: days*: 1 ○ *Duration postoperative: days*: 14 • prednisolone acetate 1% (brand name not reported) ○ *Times per day*: 4 times ○ *Duration preoperative: days*: 0 ○ *Duration postoperative: days*: 28 **Comparator: Steroids alone** • prednisolone acetate 1% (brand name not reported) ○ *Times per day*: 4 times ○ *Duration preoperative: days*: 0 ○ *Duration postoperative: days*: 28 All patients received topical gatifloxacin 0.3% 4 times a day for 28 days **Type of surgery**: Phacoemulsification
Outcomes	**Follow-up:** 1 month • Change in macular thickness • Change in macular volume • Adverse effects • Inflammation (flare)
Contact details	**Authors name:** Dr. Tae-im Kim **Institution:** Yonsei University College of Medicine **Email:** tikim@yuhs.ac **Address:** Department of Ophthalmology, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Notes	**Funding sources:** "This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology 2013R1A1A2058907)." **Declaration of interest:** "The authors have no financial conflicts of interest." **Date study conducted:** November 2013 to June 2014 **Trial registration number:** NR **Contacting study investigators:** Trial authors not contacted.

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: Not reported how list was generated. Trial was described as "randomised" but with no further details

Jung 2015 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Judgement comment: Not reported how allocation administered. Trial was described as "randomised" but with no further details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: No information on masking. We assume that in absence of reporting on this patients and personnel were not masked
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: Open-label or no information on masking. We assume that in absence of reporting on this outcome assessors were not masked
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: Follow-up not reported.
Selective reporting (reporting bias)	Unclear risk	Judgement comment: No access to protocol or trial registry entry

Kraff 1982

Methods	**Study design:** Parallel group RCT
Participants	**Country:** USA **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: 330 (NR) • *Number (%) of people followed up*: 323 (98%) • *Average age in years*: 69 • *Age range in years*: 37-91 • *Percentage women*: 60% • *Ethnic group*: NR • *Percentage with diabetes*: NR • *Percentage with uveitis*: NR **Comparator: Steroids plus placebo** • *Number of people (eyes) randomised*: 170 (NR) • *Number (%) of people followed up*: 169 (99%) • *Average age in years*: 68 • *Age range in years*: 45-97 • *Percentage women*: 54% • *Ethnic group*: NR • *Percentage with diabetes*: NR • *Percentage with uveitis*: NR **Included criteria:** Eligible for extracapsular cataract extraction with implantation of a Shearing posterior chamber lens **Excluded criteria:** NR **Pretreatment:** None noted; age, gender, follow-up and endothelial cell density preoperative compared **Eyes:** Unclear if one or both eyes included.

Kraff 1982 (*Continued*)

Interventions	**Intervention: NSAIDs plus steroids** • indomethacin (brand name not reported) ○ *Times per day*: 5 times every 10 to 15 mins 18 hrs before surgery; 1 x 12 hrs before surgery; 1 x at bedtime; 1 x 2 hrs before surgery; 1 x 1.5 hrs before surgery; 1 x 30 mins before surgery; 4 times a day postoperative ○ *Duration preoperative: days*: 1 ○ *Duration postoperative: days*: 274 • dexamethasone (in combination with neomycin sulfate, polymyxin B sulfate) for 4 days followed by dexamethasone alone for 4 weeks followed by fluorometholone for at least 6 months (Maxitrol and Maxidex) ○ *Times per day*: 4 times a day (dexamethasone) and 3 times a day (fluorometholone) ○ *Duration preoperative: days*: 1 ○ *Duration postoperative: days*: 274 **Comparator: Steroids plus placebo** • dexamethasone (in combination with neomycin sulfate, polymyxin B sulfate) for 4 days followed by dexamethasone alone for 4 weeks followed by fluorometholone for at least 6 months (Maxitrol and Maxidex) ○ *Times per day*: 4 times a day (dexamethasone) and 3 times a day (fluorometholone) ○ *Duration preoperative: days*: 1 ○ *Duration postoperative: days*: 274 • placebo (vehicle) ○ *Times per day*: 5 times every 10 to 15 mins 18 hrs before surgery; 1 x 12 hrs before surgery; 1 x at bedtime; 1 x 2 hrs before surgery; 1 x 1.5 hrs before surgery; 1 x 30 mins before surgery; 4 times a day postoperative ○ *Duration preoperative: days*: 1 ○ *Duration postoperative: days*: 274 **Type of surgery:** ECCE and phacoemulsification (unplanned ICCE n = 19 were excluded)
Outcomes	**Follow-up:** between 2.5 and 12 months. Quote: "The mean interval between surgery and angiography was 4.1 months, with a range of 2.5 to 12 months. Ninety percent of the angiograms were performed between 2.5 and 5 months after surgery, and 10% between 6 and 12 months after surgery." • Adverse effects • CMO (fluorescein angiography using Miyake 1977) • Snellen acuity only (not included in the analyses).
Contact details	**Authors name:** Manus C Kraff **Institution:** Abraham Lincoln School of Medicine, University of Illinois **Email:** NR **Address:** 5600 W. Addison Street, Chicago, IL 60634
Notes	**Funding sources:** Core Grant EY 1792 NEI Bethesda Maryland **Declaration of interest**: NR **Date study conducted:** NR **Trial registration number:** NR **Contacting study investigators**: Trial authors not contacted.

Kraff 1982 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Judgement comment: Randomisation was using a table of random numbers
Allocation concealment (selection bias)	Unclear risk	Judgement comment: Not reported how allocation administered.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement comment: Quote: "The study was double-masked; neither the physician nor the patient knew what drops the patient was receiving."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: Quote: "The study was double-masked; neither the physician nor the patient knew what drops the patient was receiving. " Quote: "The angiograms were read in a masked fashion by a retired specialist (LMJ) who had no knowledge of either the drug regimen or the type of surgical procedure."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: Some patients were excluded (n = 19) and not reported: two with vitreous loss, two with vitreous pressure and a shallow anterior chamber and 15 with possible rupture of the posterior capsule. Unclear which groups these were in. Follow-up high for visual acuity (> 95%) but lower for CMO (60% in indomethacin group versus 64% in placebo)
Selective reporting (reporting bias)	Unclear risk	Judgement comment: No access to protocol or trial registry entry

Li 2011

Methods	**Study design:** Parallel group RCT
Participants	**Country:** China **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: 104 (104) • *Number (%) of people followed up*: NR • *Average age in years*: 72 • *Age range in years*: NR • *Percentage women*: 66% • *Ethnic group*: Chinese • *Percentage with diabetes*: 100%

	• *Percentage with uveitis*: NR **Comparator: Steroids alone** • *Number of people (eyes) randomised*: 113 (113) • *Number (%) of people followed up*: NR • *Average age in years*: 72 • *Age range in years*: NR • *Percentage women*: 59% • *Ethnic group*: Chinese • *Percentage with diabetes*: 100% • *Percentage with uveitis*: NR **Included criteria:** Diabetes mellitus type 2 patients who received phacoemulsification together with artificial lens implants intervention **Excluded criteria:** Diabetic retinopathy, age-related macular degeneration, epiretinal membrane and retinal vascular disorders **Pretreatment:** Unclear if group differences. **Eyes:** One eye, unclear how selected.

Interventions	**Intervention: NSAIDs plus steroids**
	• diclofenac 1% (brand name not reported)
	  ○ *Brand name*: NR
	  ○ *Times per day*: 4 times
	  ○ *Duration preoperative: days*: 1
	  ○ *Duration postoperative: days*: 28
	• dexamethasone (combined with tobramycin) (brand name not reported)
	  ○ *Times per day*: 4 times
	  ○ *Duration preoperative: days*: 1
	  ○ *Duration postoperative: days*: 28
	Comparator: Steroids alone
	• dexamethasone (combined with tobramycin) (brand name not reported)
	  ○ *Times per day*: 4 times
	  ○ *Duration preoperative: days*: 1
	  ○ *Duration postoperative: days*: 28
	Type of surgery: Phacoemulsification

Outcomes	**Follow-up:** 1 month • CRT at follow-up (final value) • CMO (“clinically apparent”, OCT used) • Snellen acuity only (not included in analyses)
Contact details	**Authors name:** Min-Chao Li **Institution:** Department of Ophthalmology, Affiliated Nanhai Hospital of Southern Medical University, Foshan **Email:** liminchao@126.com **Address:** Department of Ophthalmology, Affiliated Nanhai Hospital of Southern Medical University, Foshan 528200, Guangdong Province, China
Notes	**Funding sources:** NR **Declaration of interest:** NR **Date study conducted:** January 2009 to December 2010

Li 2011 (*Continued*)

	Trial registration number: NR **Contacting study investigators:** Trial authors not contacted.

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: Not reported how list was generated. Trial was described as "randomised" but with no further details
Allocation concealment (selection bias)	Unclear risk	Judgement comment: Not reported how allocation administered. Trial was described as "randomised" but with no further details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: No information on masking. We assume that in absence of reporting on this patients and personnel were not masked
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: No information on masking. We assume that in absence of reporting on this patients and personnel were not masked
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: As per translation: "Unclear, not specified if there was any participant withdrawal or lost during the study period."
Selective reporting (reporting bias)	Unclear risk	Judgement comment: No access to protocol or trial registry entry

Mathys 2010

Methods	**Study design:** Parallel group RCT
Participants	**Country:** USA **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: 42 (42) • *Number (%) of people followed up*: 39 (93%) • *Average age in years*: 74 • *Age range in years*: 51-90 • *Percentage women*: 54% • *Ethnic group*: NR • *Percentage with diabetes*: 0 (excluded) • *Percentage with uveitis*: 0 (excluded) **Comparator: Steroids alone** • *Number of people (eyes) randomised*: 42 (42) • *Number (%) of people followed up*: 40 (95%)

	• *Average age in years*: 70 • *Age range in years*: 44-88 • *Percentage women*: 53% • *Ethnic group*: NR • *Percentage with diabetes*: 0 (excluded) • *Percentage with uveitis*: 0 (excluded) **Inclusion criteria:** Planning to have cataract surgery by KLC at the Ambulatory Care Center, the University of North Carolina Hospitals **Exclusion criteria:** Medically treated diabetes mellitus; history of uveitis;use of topical prostaglandin analogues for glaucoma; history of earlier intraocular surgery in the same eye; retinal vascular disease; macular degeneration;abnormal preoperative OCT measurements **Pretreatment:** Nepafenac group were slightly older, similar gender, preoperative VA, follow-up time, slightly longer phaco time **Eyes:** One eye, unclear how selected.

Interventions	**Intervention: NSAIDs plus steroids**
	• nepafenac 0.1% (brand name not reported)
	  ○ *Times per day*: 3 times
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days*: 28
	• prednisolone acetate 1% (brand name not reported)
	  ○ *Times per day*: 4 times
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days*: 28
	Comparator: Steroids alone
	• prednisolone acetate 1% (brand name not reported)
	  ○ *Times per day*: 4 times
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days*: 28
	All participants received nepafenac 0.01% drops in the operated eye thrice, 5 mins apart, immediately before surgery to maintain pupillary dilation and postoperatively, moxifloxacin 0.5% four times a day for 10 days
	Type of surgery: Phacoemulsification

Outcomes	**Follow-up:** 2 months • Change in CRT • Adverse effects • BCVA logMAR (final value)
Contact details	**Authors name:** KL Cohen **Institution:** School of Medicine, University of North Carolina **Email:** klc@med.unc.edu **Address:** Department of Ophthalmology, School of Medicine, University of North Carolina at Chapel Hill, 5100 Bioinformatics Building, 130 Mason Farm Road, CB no. 7040, Chapel Hill, NC 27599-7040, USA

Notes	**Funding sources:** "This work was supported in part by Research to Prevent Blindness, Inc., New York, NY." **Declaration of interest:** "Kenneth C Mathys and Kenneth L Cohen have no financial interest." **Date study conducted:** June 2007 to April 2008 **Trial registration number:** NCT00494494 **Contacting study investigators:** Trial authors not contacted.

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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were randomised according to the even/odd subject identification number, using computer-generated random numbers, to the control group (standard of care only) or the treatment group (standard of care plus nepafenac)."
Allocation concealment (selection bias)	Unclear risk	Judgement comment: Not reported how allocation administered.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "were consecutively enrolled in this randomised, non-masked, parallel-group clinical trial. " Judgement comment: Participants were not masked.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "At the 2 months visit, technicians, who were masked to treatment, measured ETDRS BCVA, and OCT scans were performed." Judgement comment: Experienced ophthalmic photographers, who were masked to treatment, obtained Stratus OCT (Carl Zeiss Meditec, Inc., San Francisco, CA, USA) scans using the fast macular thickness protocol
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The mean time to follow-up was 73.31 days (± 21.58 SD, range 55-146) in the treatment group and 68.98 days (± 13.98, range 50-120) in the standard-of- care group." Judgement comment: 39/42 (93%) of intervention group and 40/42 (95%) of comparator group followed-up. Missing data less than 20% (i.e. more than 80% follow-up) and equal follow-up in both groups and no obvious reason why loss to follow-up should be related to outcome

Mathys 2010 (*Continued*)

Selective reporting (reporting bias)	Low risk	Judgement comment: Outcomes on trial registry entry were reported

Miyake 2007

Methods	**Study design:** Randomised control trial
Participants	**Country:** Japan **Setting:** Eye hospital **Intervention: NSAIDs alone** • *Number of people (eyes) randomised*: 31 (31) • *Number (%) of people followed up*: 25 (81%) • *Average age in years*: 65 • *Age range in years*: NR • *Percentage women*: 48% • *Ethnic group*: NR • *Percentage with diabetes*: 0 (excluded) • *Percentage with uveitis*: 0 (excluded) **Comparator: Steroids alone** • *Number of people (eyes) randomised*: 31 (31) • *Number (%) of people followed up*: 25 (81%) • *Average age in years*: 66 • *Age range in years*: NR • *Percentage women*: 60% • *Ethnic group*: NR • *Percentage with diabetes*: 0 (excluded) • *Percentage with uveitis*: 0 (excluded) **Inclusion criteria:** Age 50 to 70 years; subjected for unilateral surgery or to have 6 months' span between surgeries in patients with bilateral cataract **Exclusion criteria:** Eyes encountering acute ocular infection or inflammation during the first month of the study; eyes showing sensitivity to diclofenac or fluorometholone; eyes showing sensitivity to fluorescein sodium; eyes with insufficient dilation, (pupil diameter 4 mm) and with hazy media affecting laser Doppler flowmetry (LDF); eyes with history of other ocular surgeries; eyes with pseudoexfoliation syndrome; history of trauma; uveitis, glaucoma or other disorders; complication of diabetes and kidney disorders; heart failure, cardiac infarction, and cerebrovascular disease; uncontrollable hypertension; rupture of the posterior capsule, vitreous loss, and other complications during a cataract/IOL implantation procedure **Pretreatment:** No major imbalances; compared age and sex. **Eyes:** One eye, unclear how selected.
Interventions	**Intervention: NSAIDs alone** • diclofenac 0.1% (Diclod, Wakamoto, Tokyo, Japan) ○ *Times per day*: 4 times on day of surgery (3, 2, 1, 0.5 hrs before surgery); 3 times a day postoperative ○ *Duration preoperative: days*: 0 ○ *Duration postoperative: days*: 35 **Comparator: Steroids alone**

	• fluorometholone 0.1% (Flumethrone, Santen, Osaka, Japan) ○ *Times per day*: 4 times on day of surgery (3, 2, 1, 0.5 hrs before surgery); 3 times a day postoperative ○ *Duration preoperative: days*: on day of surgery ○ *Duration postoperative: days*: 35 Quote "Other topical drugs used before and after surgery included mydriatics and antibiotics only." **Type of surgery:** Phacoemulsification
Outcomes	**Follow-up:** 5 weeks • CMO (fluorescein angiography using Miyake 1977 classification) • Inflammation (mean aqueous flare, ?units) • Snellen acuity only, not included in the analysis
Contact details	**Authors name:** Kensaku Miyake **Institution:** Shohzankai Medical Foundation, Miyake Eye Hospital **Email:** miyake@spice.or.jp **Address:** Miyake Eye Hospital, 3-15-68, Ozone, Kita-ku, Nagoya 462-0825, Japan
Notes	**Funding sources:** NR **Declaration of interest**: Reported none for all authors. **Date study conducted:** NR **Trial registration number:** NR **Contacting study investigators:** Trial authors not contacted.

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Each patient was randomly assigned to one of the two groups by one of the authors (SA), using the envelope method." Judgement comment: Not reported how list was generated.
Allocation concealment (selection bias)	Unclear risk	Quote: "Each patient was randomly assigned to one of the two groups by one of the authors (SA), using the envelope method." Judgement comment: Reported that envelopes used but unclear if they were sequentially numbered, sealed, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Judgement comment: Study described as being "conducted in a prospective, double-masked, randomised manner." Patients probably masked not clearly described

Miyake 2007 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: Fluorescein angiography and laser flarimetry assessed by masked observers and analysis was masked
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: 25/31 (80%) of eyes in both groups were followed up and reasons for loss to follow-up did not appear to be related to outcome
Selective reporting (reporting bias)	Unclear risk	Judgement comment: No access to protocol or trial registry entry

Miyake 2011

Methods	**Study design:** Parallel group RCT
Participants	**Country:** Japan **Setting:** Eye hospital **Intervention: NSAIDs alone** • *Number of people (eyes) randomised*: 30 (30) • *Number (%) of people followed up*: 28 (93%) • *Average age in years*: 64 • *Age range in years*: 48-82 • *Percentage women*: 47% • *Ethnic group*: NR • *Percentage with diabetes*: 7% • *Percentage with uveitis*: 0% (excluded) **Comparator: Steroids alone** • *Number of people (eyes) randomised*: 30 (30) • *Number (%) of people followed up*: 27 (90%) • *Average age in years*: 66 • *Age range in years*: 37-83 • *Percentage women*: 45% • *Ethnic group*: NR • *Percentage with diabetes*: 10% • *Percentage with uveitis*: 0% (excluded) **Inclusion criteria:** Aged over 20 years; phacoemulsification cataract extraction and IOL implantation between October 2007 and April 2008 at Shohzankai Medical Foundation, Miyake Eye Hospital **Exclusion criteria:** Systemic, topical, or ointment steroidal agents within 14 days of surgery; had had an intraocular or periocular injection of steroidal agents within 90 days of surgery; had taken systemic or topical NSAIDs within 7 days of surgery; had a history of ophthalmic surgery (including laser surgery) or of ocular trauma that could affect the study results; had pseudoexfoliation syndrome; had a history of chronic or recurring ocular inflammation (e.g. uveitis or scleritis); had diabetic retinopathy; had an ocular anomaly (e.g. aniridia, congenital cataract); had iris atrophy; had disorders that would preclude improvement in visual function; had macular oedema; had severe

	corneal epithelial disorder (e.g. corneal ulcer); had no visual function in the contralateral eye; were scheduled to have other ocular surgery from baseline to 5 weeks after cataract surgery; had secondary IOL implantation, were allergic to or might have been sensitive to NSAIDs, amfenac, or fluorometholone; had a positive skin reaction to fluorescein; had a tendency to bleed or were currently on anticoagulants; had had prostaglandin-type treatment for glaucoma within 4 days of surgery; had been included in a previous study of prostaglandin type antiglaucoma drugs; had joined another clinical study within 30 days of the study; had ocular infection, had uncontrollable diabetes mellitus; had severe liver, kidney, or heart disorder; might have been pregnant or were currently breastfeeding; had other factors determined to be unsuitable for the study **Pretreatment:** No major imbalances. **Eyes:** One eye, unclear how selected.
Interventions	**Intervention: NSAIDs alone** • nepafenac 0.1% (Nevanec) ○ *Times per day*: 3 times a day except for day of surgery 4 times ○ *Duration preoperative: days*: 1 ○ *Duration postoperative: days*: 35 **Comparator: Steroids alone** • fluorometholone 0.1% (Flucon) ○ *Times per day*: 3 times a day except for day of surgery 4 times ○ *Duration preoperative: days*: 1 ○ *Duration postoperative: days*: 35 Levofloxacin ophthalmic solution 0.5% (Cravit) was applied to each eye 5 times before surgery and 3 times a day after surgery for 2 weeks **Type of surgery:** Phacoemulsification
Outcomes	**Follow-up:** 5 weeks • Change in CRT • Adverse effects • CMO (fluorescein angiography using Miyake 1977 classification) • Inflammation (mean flare, photons/millisecond)
Contact details	**Authors name:** K Miyake **Institution:** Shohzankai Medical Foundation, Miyake Eye Hospital (K.Miyake, Ota, G. Miyake), Nagoya, and TokyoMetropolitan Geriatric Hospital (Numaga), Tokyo, Japan **Email:** miyake@spice.or.jp **Address:** Shohzankai Medical Foundation, Miyake Eye Hospital, 3-15-68, Ozone, Kita-ku, Nagoya, 462-0825, Japan
Notes	**Funding sources:** NR **Declaration of interest**: "Drs. Miyake and Numaga are consultants to Alcon Japan Ltd. " **Date study conducted:** October 2007 to April 2008 **Trial registration number**: NR **Contacting study investigators:** Primary investigator emailed to confirm how patients allocated

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

Miyake 2011 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: Not reported how list was generated. Trial was described as "randomised" but with no further details
Allocation concealment (selection bias)	Unclear risk	Quote: "The 2 drugs had identical outer appearances and could not be differentiated. The same physician (J.N.) served as the medical monitor and assigned 1 of the drugs to each patient." Judgement comment: Unclear if allocation concealed from person recruiting participants
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Judgement comment: Described as "double-blind" with no information on who was masked
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Judgement comment: Described as "double-blind" with no information on who was masked
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: Missing data less than 20% (i.e. more than 80% follow-up) and equal follow-up in both groups and no obvious reason why loss to follow-up should be related to outcome: 28/30 (93%) in nepafenac group and 27/30 (90%) in the fluorometholone group
Selective reporting (reporting bias)	Unclear risk	Judgement comment: No access to protocol or trial registry entry

Miyanaga 2009

Methods	**Study design:** Parallel group RCT
Participants	**Country:** Japan **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: 24 (NR) • *Number (%) of people followed up*: NR • *Average age in years*: 71 • *Age range in years*: 46-86 • *Percentage women*: 71% • *Ethnic group*: NR • *Percentage with diabetes*: 0 (excluded) • *Percentage with uveitis*: 0 (excluded) **Intervention: NSAIDs alone** • *Number of people (eyes) randomised*: 25 (NR)

	• *Number (%) of people followed up*: NR • *Average age in years*: 74 • *Age range in years*: 48-86 • *Percentage women*: 68% • *Ethnic group*: NR • *Percentage with diabetes*: 0 (excluded) • *Percentage with uveitis*: 0 (excluded) **Comparator: Steroids alone** • *Number of people (eyes) randomised*: 23 (NR) • *Number (%) of people followed up*: NR • *Average age in years*: 70 • *Age range in years*: 41-83 • *Percentage women*: 74% • *Ethnic group*: NR • *Percentage with diabetes*: 0 (excluded) • *Percentage with uveitis*: 0 (excluded) **Inclusion criteria:** Scheduled to undergo routine phacoemulsification combined with IOL **Exclusion criteria:** Corneal disease; glaucoma; uveitis; pseudoexfoliation syndrome; diabetes; other pathologies that might affect treatment responses or evaluations; systemic or topical anti-inflammatory therapy within 1 month prior to surgery **Pretreatment:** Quote: "There were no significant differences between groups in gender or age." **Eyes:** Probably one eye only included in the trial but not clearly reported and unclear how selected

Interventions	**Intervention: NSAIDs plus steroids**
	• bromfenac 0.1% (Bronuck; Senju Pharmaceutical Co.,Osaka, Japan)
	  ○ *Times per day*: twice a day
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days*: 56
	• betamethasone 0.1% for 28 days and fluorometholone for 28 days (Rinderon, Shionogi Pharmaceutical, Japan, and Flumetholon, Santen Pharmaceutical co)
	  ○ *Times per day*: 4 times
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days*: 56
	Intervention: NSAIDs alone
	• bromfenac 0.1% (Bronuck; Senju Pharmaceutical Co.,Osaka, Japan)
	  ○ *Times per day*: twice a day
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days*: 56
	Comparator: Steroids alone
	• betamethasone 0.1% for 28 days and fluorometholone for 28 days (Rinderon, Shionogi Pharmaceutical Co., Osaka, Japan, and Flumetholon, Santen Pharmaceutical Co)
	  ○ *Times per day*: 4 times
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days*: 56
	All participants received 0.5% levofloxacin eyedrops four times daily until 2 months

	after surgery, and 0.5% tropicamide and 0.5% phenylephrinehydrochloride once daily for 2 weeks **Type of surgery:** Phacoemulsification
Outcomes	**Follow-up:** 2 months • Adverse effects • CMO ("obvious CMO confirmed by OCT") • Inflammation (aqueous flare, photons/millisecond)
Contact details	**Authors name:** Masaru Miyanaga **Institution:** Miyata Eye Hospital **Email:** miyanaga@miyata-med.ne.jp **Address:** Miyata Eye Hospital, 6-3 Kurahara, Miyakonojo, Miyazaki 885-0051, Japan
Notes	**Funding sources:** NR **Declaration of interest:** NR **Date study conducted:** February 2006 to August 2006 **Trial registration number:** NR **Contacting study investigators:** Trial authors not contacted.

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: Not reported how list was generated. Trial was described as "randomised" but with no further details
Allocation concealment (selection bias)	Unclear risk	Judgement comment: Not reported how list was generated. Trial was described as "randomised" but with no further details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: No information on masking. We assume that in absence of reporting on this patients and personnel were not masked
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: No information on masking. We assume that in absence of reporting on this outcome assessors were not masked
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: Only 1 patient was withdrawn from the study from the steroid only group due to CMO 1 month postop. Otherwise follow-up not reported
Selective reporting (reporting bias)	Unclear risk	Judgement comment: No access to protocol or trial registry entry

Moschos 2012

Methods	**Study design:** Parallel group RCT
Participants	**Country:** Greece **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: 38 (38) • *Number (%) of people followed up*: NR • *Average age in years*: 77 • *Age range in years*: NR • *Percentage women*: 68% • *Ethnic group*: NR • *Percentage with diabetes*: 0 (excluded) • *Percentage with uveitis*: 0 (excluded) **Comparator: Steroids alone** • *Number of people (eyes) randomised*: 41 (41) • *Number (%) of people followed up*: NR • *Average age in years*: 77 • *Age range in years*: NR • *Percentage women*: 63% • *Ethnic group*: NR • *Percentage with diabetes*: 0 (excluded) • *Percentage with uveitis*: 0 (excluded) **Inclusion criteria:** Patients requiring phacoemulsification cataract surgery. **Exclusion criteria:** Presence of corneal abnormalities; history of intraocular surgery; preoperative ECC < 1500 cells/mm^2; history of uveitis, diabetes, and age-related macular degeneration; regular, systemic use of steroid or NSAIDs during the previous 3 months; and intraoperative complications, such as posterior capsule rupture, vitreous loss, lost nucleus, zonule dehiscence, and wound leak **Pretreatment:** No major imbalances noted. **Eyes:** One eye, unclear how selected.

Interventions	**Intervention: NSAIDs plus steroids**
	• diclofenac sodium 0.1% (Denaclof, Novartis Hellas, Athens, Greece)
	  ◦ *Times per day*: 3 times
	  ◦ *Duration preoperative: days*: 3
	  ◦ *Duration postoperative: days*: 28
	• dexamethasone sodium phosphate 0.1% (combined with chloramphenicol 0.5%) (Dispersadron (Novartis Hellas, Athens, Greece)
	  ◦ *Times per day*: 4 times
	  ◦ *Duration preoperative: days*: 0
	  ◦ *Duration postoperative: days*: 28
	Comparator: Steroids alone
	• dexamethasone sodium phosphate 0.1% (combined with chloramphenicol 0.5%) (Dispersadron, Novartis Hellas, Athens, Greece)
	  ◦ *Times per day*: 4 times
	  ◦ *Duration preoperative: days*: 0
	  ◦ *Duration postoperative: days*: 28
	Type of surgery: Phacoemulsification

Moschos 2012 (*Continued*)

Outcomes	**Follow-up:** 1 month • CRT at follow-up (final value) • BCVA logMAR (final value)
Contact details	**Authors name:** Irini P. Chatziralli **Institution:** Department of Ophthalmology University of Athens **Email:** eirchat@yahoo.gr **Address:** Department of Ophthalmology, University of Athens, 28 Papanastasiou street 17342 Athens, Greece
Notes	**Funding sources:** NR **Declaration of interest:** "No competing financial interests exist." **Date study conducted:** NR **Trial registration number:** NR **Contacting study investigators:** Trial authors not contacted.

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised (through random number generation) to 1 of the 2 postoperative treatment arms."
Allocation concealment (selection bias)	Unclear risk	Judgement comment: Not reported how allocation administered. Trial described as "randomised" but with no further details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: No information on masking. We assume that in absence of reporting on this patients and personnel were not masked
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: No information on masking. We assume that in absence of reporting on this patients and personnel were not masked
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: Follow-up not reported.
Selective reporting (reporting bias)	Unclear risk	Judgement comment: No access to protocol or trial registry entry

Quentin 1989

Methods	**Study design:** Parallel group RCT
Participants	**Country:** Germany **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: 90 (90) • *Number (%) of people followed up*: 57 (63%) • *Average age in years*: 73 (,median) • *Age range in years*: NR • *Percentage women*: 53% • *Ethnic group*: NR • *Percentage with diabetes*: NR (diabetic retinopathy excluded) • *Percentage with uveitis*: 0 (excluded) **Comparator: Steroids plus placebo** • *Number of people (eyes) randomised*: 89 (89) • *Number (%) of people followed up*: 55 (62%) • *Average age in years*: 73 (median) • *Age range in years*: NR • *Percentage women*: 57% • *Ethnic group*: NR • *Percentage with diabetes*: NR (diabetic retinopathy excluded) • *Percentage with uveitis*: 0 (excluded) **Inclusion criteria:** No complication during surgery; fluorescein angiography can be done; compliance of the patient is very probable **Exclusion criteria:** Exudative maculopathy; diabetic retinopathy; prior uveitis; glaucoma; allergic reaction on fluorescein angiography; systemic steroid treatment; therapy with non-steroid antiphlogistics; treatment with anticoagulation **Pretreatment:** Age and gender comparable. **Eyes:** One eye, unclear how selected.
Interventions	**Intervention: NSAIDs plus steroids** • diclofenac 0.1% (Voltaren ophtha, Civa-Geigy AG and Naclof Dispersa AG) ◦ *Times per day*: 5 times 2 drops preoperative and 3 x 1 drop postoperative; then 5 times a day and after discharge 3 times a day. ◦ *Duration preoperative: days*: 0 ◦ *Duration postoperative: days*: 180 • dexamethasone (brand name not reported) ◦ *Brand name*: NR ◦ *Times per day*: 4 times a day; 5 times a day; 3 times a day after discharge ◦ *Duration preoperative: days*: 0 ◦ *Duration postoperative: days*: 42 **Comparator: Steroids plus placebo** • dexamethasone (brand name not reported) ◦ *Times per day*: 4 times a day; 5 times a day; 3 times a day after discharge ◦ *Duration preoperative: days*: 0 ◦ *Duration postoperative: days*: 42 • placebo (not specified) ◦ *Times per day*: 5 x 2 drops preoperative and 3 x 1 drop postoperative; then 5 times a day and after discharge 3 times a day.

Quentin 1989 (*Continued*)

	○ *Duration preoperative: days*: 0 ○ *Duration postoperative: days*: 180 All participants received antibiotic eye drops for the first 4 days after surgery **Type of surgery:** ICCE
Outcomes	**Follow-up:** not reported, assume 180 days as this is duration of treatment • Adverse effects • CMO (fluorescein angiography using Miyake 1977 classification) • BCVA Snellen only, not included in the analyses
Contact details	**Authors name:** CD Quentin **Institution:** Uni Augenklinik Göttingen **Email:** NR **Address:** Uni Augenklinik GöttingenRobert-Koch-Straße 40, D-3400 Göttingen, Germany
Notes	**Funding sources:** NR **Declaration of interest:** NR **Date study conducted:** NR **Trial registration number:** NR **Contacting study investigators:** Not contacted

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: Not reported how list was generated. Trial was described as "randomised" but with no further details
Allocation concealment (selection bias)	Unclear risk	Judgement comment: Not reported how allocation administered. Trial was described as "randomised" but with no further details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Judgement comment: Described as "double-blind" with no information on who was masked
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Judgement comment: Described as "double-blind" with no information on who was masked
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: Follow-up missing data > 20% but follow-up equal in both groups: 57/90 (63%) followed up in diclofenac group and 55/89 (62%) in the placebo group

Selective reporting (reporting bias)	Unclear risk	Judgement comment: No access to protocol or trial registry entry

Rossetti 1996

Methods	**Study design:** Parallel group RCT
Participants	**Country:** Italy **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: 42 • *Number (%) of people followed up*: NR • *Average age in years*: 74 • *Age range in years*: NR • *Percentage women*: 71 • *Ethnic group*: NR • *Percentage with diabetes*: 0 • *Percentage with uveitis*: NR **Comparator: Steroids plus placebo** • *Number of people (eyes) randomised*: 46 • *Number (%) of people followed up*: NR • *Average age in years*: 73 • *Age range in years*: NR • *Percentage women*: 57 • *Ethnic group*: NR • *Percentage with diabetes*: 0 • *Percentage with uveitis*: NR **Inclusion criteria:** Extracapsular cataract extraction (ECCE) with implantation of an IOL **Exclusion criteria:** Diabetes; glaucoma; maculopathy; on systemic steroids, acetazolamide, or NSAIDs **Pretreatment:** Age, gender and preoperative visual acuity were compared. Higher proportion of women in the diclofenac group (71%) compared with the placebo group (57%). Otherwise groups were similar **Eyes:** Probably one eye only included in the trial but not clearly reported and unclear how selected

Interventions	**Intervention: NSAIDs plus steroids**
	• diclofenac sodium (Voltaren®)
	  ○ *Times per day*: 4 times
	  ○ *Duration preoperative: days*: 3
	  ○ *Duration postoperative: days*: 90
	• dexamethasone (combined with tobramycin) (brand name not reported)
	  ○ *Times per day*: 4 times
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days:* 21
	Comparator: Steroids plus placebo
	• dexamethasone (combined with tobramycin) (brand name not reported)

Rossetti 1996 (*Continued*)

	○ *Times per day*: 4 times ○ *Duration preoperative: days:* 0 ○ *Duration postoperative: days:* 21 • placebo (unspecified) ○ *Times per day*: 4 times ○ *Duration preoperative: days:* 3 ○ *Duration postoperative: days:* 90 **Type of surgery:** ECCE
Outcomes	**Follow-up:** 6 months • Adverse effects • CMO (fluorescein angiography using Miyake 1977 classification) • Snellen acuity only, not included in analyses
Contact details	**Authors name:** Nicola Orzalesi **Institution:** Clinica Oculistica Universitti di Milano, Istituto di Scienze Biomediche, Ospedale San Paolo **Email:** NR **Address:** Clinica Oculistica Universitti di Milano, Istituto di Scienze Biomediche, Ospedale San Paolo, Via di Rudini 8,20142 Milano, Italy
Notes	**Funding sources**: NR **Declaration of interest:** None of the authors has a proprietary interest in the instruments or materials mentioned **Date study conducted:** NR **Trial registration number:** NR **Contacting study investigators:** Trial authors not contacted.

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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Judgement comment: Randomisation was obtained using a table of random numbers
Allocation concealment (selection bias)	Unclear risk	Judgement comment: Not reported how allocation administered. Trial described as "randomised" but with no further details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Judgement comment: Not reported how allocation administered. Trial described as "double-masked" but with no further details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Judgement comment: anterior chamber cell and flare and fluorescein angiography was performed by masked evaluations. No indication if the rest of the exam (visual acuity assessment (Snellen chart), slit- lamp biomicroscopy, IOP measurement by applanation tonometry, and ophthalmoscopic eval-

Rossetti 1996 (*Continued*)

		uation was performed by masked evaluators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: Follow-up not explicitly reported. However, demonstrated in several tables (such as in Table 5 (% of patients in the calculation of mean (SD) postoperative VA)). None of these were < 80%
Selective reporting (reporting bias)	Unclear risk	Judgement comment: No access to protocol or trial registry entry

Singh 2012

Methods	**Study design:** Parallel group RCT
Participants	**Country:** USA **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: 133 (133) • *Number (%) of people followed up*: 125 (94%) • *Average age in years*: 67 • *Age range in years*: 39-87 • *Percentage women*: 66% • *Ethnic group*: white 78%; black 17% • *Percentage with diabetes*: 100% • *Percentage with uveitis*: 0 (excluded) **Comparator: Steroids plus placebo** • *Number of people (eyes) randomised*: 130 (130) • *Number (%) of people followed up*: 126 (97%) • *Average age in years*: 66 • *Age range in years*: 32-84 • *Percentage women*: 60% • *Ethnic group*: white 86%; black 10% • *Percentage with diabetes*: 100% • *Percentage with uveitis*: 0 (excluded) **Inclusion criteria:** Diabetic (type 1 or type 2); 18 years and older; existing diagnosis of nonproliferative diabetic retinopathy that required cataract extraction with planned implantation of a posterior chamber IOL; at least 50% of all enrolled patients were required to have moderate to severe nonproliferative diabetic retinopathy, as defined by the International Clinical Diabetic Retinopathy Disease Severity Scale 2 **Exclusion criteria:** Significant corneal staining scores at baseline; history of dry eye syndrome; other conditions that may have caused macular oedema, including pre-existing histories of retinal vein occlusions, ocular surgeries, inflammatory eye diseases, ocular infections, congenital ocular anomalies, and ocular traumas; central subfield macular thickness 250 microns or more; baseline cysts, and the presence of macular traction and epiretinal membranes; use of concomitant medications such as topical or systemic NSAIDs and steroids **Pretreatment:** No major group differences. Compared age, gender, ethnic group, iris

	colour, NPDR classification. visual acuity **Eyes:** One eye, unclear how selected.
Interventions	**Intervention: NSAIDs plus steroids** • nepafenac 1% (Nevanac®; Alcon Research Ltd, Fort Worth, TX) ○ T*imes per day*: 3 times ○ *Duration preoperative: days*: 1 ○ *Duration postoperative: days*: 90 • prednisolone acetate (Omnipred, Alcon) ○ T*imes per day*: 4 times ○ *Duration preoperative: days:* 0 ○ *Duration postoperative: days:* 14 **Comparator: Steroids plus placebo** • prednisolone acetate (Omnipred, Alcon) ○ *Times per day*: 4 times ○ *Duration preoperative: days:* 0 ○ *Duration postoperative: days:* 14 • placebo (vehicle) ○ *Times per day*: 3 times; one drop prior to surgery ○ *Duration preoperative: days:* 1 ○ *Duration postoperative: days:* 90 **Interventions** Approximately one-third of the patients were instructed, based on the opinion of the investigator, to use steroids for more than 2 weeks postsurgery **Type of surgery:** NR but presumably was phacoemulsification as USA study conducted 2008
Outcomes	**Follow-up:** 90 days • Change in CRT (Quote: "Mean maximum change in central subfield macular thickness measurement") • Adverse effects • CMO (Quote ">= 30% increase in central subfield macular thickness from baseline" using OCT) • Inflammation (flare mentioned but data not reported) • BCVA (loss of more than 5 letters from day 7 postoperative)
Contact details	**Authors name:** Rishi Singh **Institution:** Cole Eye Institute, Cleveland Clinic Foundation, **Email:** drrishisingh@gmail.com **Address:** Cole Eye Institute, Cleveland Clinic Foundation, 9500 Euclid Avenue, i-32 Cleveland, OH 44195, USA
Notes	**Funding sources:** NR **Declaration of interest:** "RS, LA, GJJ, RPL, JL, HJR, KS, and TW are paid consultants for Alcon Research Ltd (Fort Worth, TX). DS is an employee of Alcon Research, Ltd. Medical writing support, which was funded by Alcon Research Ltd, was provided by Cullen T Vogelson and Usha Sivaprasad, of Illuminated Research LLC (Fort Worth, TX) ." **Date study conducted:** November 2008 and July 2010

Singh 2012 (*Continued*)

	Trial registration number: NCT00782717 **Contacting study investigators:** Trial authors not contacted.

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "This was a multicenter, randomised, double-masked, vehicle-controlled, parallel-group study" Judgement comment: Not reported how list was generated.
Allocation concealment (selection bias)	Unclear risk	Judgement comment: Not reported how allocation administered. Trial described as "randomised" but with no further details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement comment: Study was double-masked with a placebo consisting of vehicle only. It was not clearly stated whether the masking was likely to have been effective but we have assumed that it was
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: Study was double-masked with a placebo consisting of vehicle only. It was not clearly stated whether the masking was likely to have been effective but we have assumed that it was Quote: "Total macular volume was determined from a 6 mm diameter circle centered on the foveal center. Morphological features, including intraretinal cysts, were analyzed by the reading center in a masked fashion."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: 125/133 (94%) in nepafenac group included in the analysis compared with 126/130 (97%) in control group. Missing data less than 20%. 95%-96% of patients enrolled included in final analysis. However, 8 patients in the Nepafenac group and 4 patients in the Vehicle group excluded from final analysis. Reasons not clearly explained
Selective reporting (reporting bias)	Low risk	Judgement comment: Outcomes on trial registry entry were reported

Solomon 1995

Methods	**Study design:** Parallel group RCT
Participants	**Country:** Canada (8 sites) and Germany (2 sites) **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: 226 (226) • *Number (%) of people followed up at days 21 to 60*: 118 (52%) • *Number (%) of people followed up at days:* 126 (56%) • *Average age in years*: 67 • *Age range in years*: 39-99 • *Percentage women*: 50% • *Ethnic group*: 95% white • *Percentage with diabetes*: NR • *Percentage with uveitis*: NR **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: 234 (234) • *Number (%) of people followed up at days 21 to 60*: 134 (57%) • *Number (%) of people followed up at days 121 to 240*: 144 (62%) • *Average age in years*: 69 • *Age range in years*: 40-100 • *Percentage women*: 53% • E*thnic group 94% white* • *Percentage with diabetes*: NR • *Percentage with uveitis*: NR **Comparator: Steroids plus placebo** • *Number of people (eyes) randomised*: 221 (221) • *Number (%) of people followed up at days 21 to 60*: 112 (51%) • *Number (%) of people followed up at days 121 to 240*: 114 (52%) • *Number (%) of people followed up* : See below • *Average age in years*: 68 • *Age range in years*: 26-99 • *Percentage women*: 56 • *Ethnic group 92% white* • P*ercentage with diabetes*: NR • *Percentage with uveitis*: NR **Inclusion criteria:** Unilateral extracapsular cataract extraction (by manual nuclear expression) with posterior chamber lens implantation **Exclusion criteria:** Taking aspirin, topical epinephrine, systemic or topical cyclo-oxygenase inhibitors, or oral corticosteroid; allergic to cyclo-oxygenase inhibitors; history of chronic intraocular inflammation; pre-existing macular pathology; history of herpetic keratitis; corneal or vitreous opacity; non-compliant patients **Pretreatment:** No major imbalances in age, gender, ethnic group. **Eyes:** One eye, this was the eye scheduled for unilateral extracapsular cataract extraction

Interventions	**Intervention: NSAIDs plus steroids**
	• flurbiprofen 0.03% (Ocufen, Ocufur)
	  ○ *Times per day*: 4 times a day and 4 drops before surgery
	  ○ *Duration preoperative: days*: 2
	  ○ *Duration postoperative: days*: 90
	• prednisolone acetate 1 % or dexamethasone sodium phosphate 0.1 % (brand

	name not reported) ○ *Times per day*: NR ○ *Duration preoperative: days*: NR ○ *Duration postoperative: days*: NR **Intervention: NSAIDs plus steroids** • indomethacin 1% (Indocid) ○ *Times per day*: 4 times a day and 4 drops before surgery ○ *Duration preoperative: days*: 2 ○ *Duration postoperative: days*: 90 • prednisolone acetate 1% or dexamethasone sodium phosphate 0.1% (brand name not reported) ○ *Times per day*: NR ○ *Duration preoperative: days*: NR ○ *Duration postoperative: days*: NR **Comparator: Steroids plus placebo** • prednisolone acetate 1% or dexamethasone sodium phosphate 0.1% (brand name not reported) ○ *Times per day*: NR ○ *Duration preoperative: days:* NR ○ *Duration postoperative: days:* NR • placebo (flurbiprofen vehicle) ○ *Times per day*: 4 times a day and 4 drops before surgery ○ *Duration preoperative: days*: 2 ○ *Duration postoperative: days*: 90 Duration postoperative: days - the investigator had the option of extending the treatment for an additional 3 months. This option was chosen for 10.9% (25/230) of vehicle-treated patients, 8.4% (20/238) of flurbiprofen-treated patients, and 9.7% (22/227) of indomethacin-treated patients. Concomitant medications included aminoglycoside antibiotics (100% of patients) and topical corticosteroids (prednisolone acetate 1% or dexamethasone sodium phosphate 0.1%) in 88.7% (204/230) of vehicle treated patients, 87.8% (209/238) of flurbiprofen treated patients, and 88.1% (200/227) of indomethacin-treated patients **Type of surgery:** ECCE
Outcomes	**Follow-up:** 6 months • Poor vision outcome due to MO (angiographic CME plus visual acuity <=20/40) • Adverse effects • CMO (fluorescein angiography 0 = no visible macular oedema; 1 = oedema without clear cut cystoid spaces; 2 = oedema with clearly evident cystoid spaces; 3 = florid oedema with cystoid spaces; CME = grades 1 to 3) • BCVA (Snellen acuity but not reported by treatment group)
Contact details	**Authors name:** Leon D Solomon **Institution:** NR **Email:** NR **Address:** NR
Notes	**Funding sources:** Supported by Allergan, Inc., Irvine California **Declaration of interest:** None of the Flurbiprofen-CME Study Group members has a

	commercial or proprietary interest in 0.03% flurbiprofen or 1% indomethacin **Date study conducted:** NR **Trial registration number:** NR **Contacting study investigators:** Trial authors not contacted.

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported how list was generated. Trial was described as "randomised" but with no further details
Allocation concealment (selection bias)	Unclear risk	Judgement comment: Not reported how allocation administered. Trial was described as "randomised, double-masked" but with no further details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Judgement comment: Described as "double-masked". Medications were masked and fluorescein angiograms were read in a masked fashion by 2 retinal specialists. Uncertain if the operating surgeons or clinicians involved in follow-up were masked to the allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Judgement comment: Each fluorescein angiogram was read in a masked fashion by two retinal specialists. Unclear if treating ophthalmologists involved in other aspects of patient care were also masked
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: Follow-up: 177/226 (78%) in flurbiprofen group, 177/234 (76%) in indomethacin group, 160/221 (72%) in placebo group. Reasons for loss to follow-up not described
Selective reporting (reporting bias)	High risk	Judgement comment: No access to protocol or trials registry entry. Not all follow-up points were reported fully

Tauber 2006

Methods	**Study design:** Parallel group RCT
Participants	**Country:** USA **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: NR • *Number (%) of people followed up*: 16 (NR) • *Average age in years*: NR

	• *Age range in years*: NR • *Percentage women*: NR • *Ethnic group*: NR • *Percentage with diabetes*: NR • *Percentage with uveitis*: NR **Comparator: Steroids alone** • *Number of people (eyes) randomised*: NR • *Number (%) of people followed up*: 16 (NR) • *Average age in years*: NR • *Age range in years*: NR • *Percentage women*: NR • *Ethnic group*: NR • *Percentage with diabetes*: NR • *Percentage with uveitis*: NR **Inclusion criteria:** NR **Exclusion criteria:** NR **Pretreatment:** Groups differences not reported. **Eyes:** Unclear if one or both eyes included.

Interventions	**Intervention: NSAIDs plus steroids**
	• ketorolac tromethamine 0.4% (Acular LS)
	  ○ *Times per day*: 4 times
	  ○ *Duration preoperative: days*: 1
	  ○ *Duration postoperative: days*: 30
	• prednisolone acetate 1% (ECONOPRED PLUS®)
	  ○ *Times per day*: 4 times
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days*: 7 plus taper
	Comparator: Steroids alone
	• prednisolone acetate 1% (ECONOPRED PLUS®
	  ○ *Times per day*: 4 times
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days*: 7 plus taper
	Type of surgery: NR

Outcomes	**Follow-up:** 30 days (3 month follow-up mentioned but not reported) • Change in CRT (but mean/SD not reported) • Proportion with > 10% increase in retinal thickness
Contact details	**Authors name:** S Tauber **Institution:** Ophthalmology, St. John's Hospital and Clinics, Springfield, MO **Email:** NR **Address:** Ophthalmology, St. John's Hospital and Clinics, Springfield, MO
Notes	**Funding sources:** Alcon Laboratories, Inc. **Declaration of interest**: "Commercial Relationships S. Tauber, Alcon, F; Alcon, R; J. Gessler, None; W. Scott, None; C. Peterson, None; P. Hamlet, None." **Date study conducted:** NR **Trial registration number:** NR

Tauber 2006 (*Continued*)

	Contacting study investigators: Abstract only, authors contacted by email regarding publication of full study results but no reply

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: Not reported how list was generated. Trial was described as "randomised" but with no further details
Allocation concealment (selection bias)	Unclear risk	Judgement comment: Not reported how allocation administered. Trial was described as "randomised" but with no further details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: No information on masking. We assume that in absence of reporting on this patients and personnel were not masked
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: No information on masking. We assume that in absence of reporting on this outcome assessors were not masked
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: Follow-up not reported.
Selective reporting (reporting bias)	High risk	Judgement comment: Some outcomes not reported including 3-month OCT outcomes

Ticly 2014

Methods	**Study design:** Parallel group RCT
Participants	**Country:** Brazil **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: 42 (42) • *Number (%) of people followed up*: 37 (88) • *Average age in years*: 67 • *Age range in years*: NR • *Percentage women*: 43 • *Ethnic group*: NR • *Percentage with diabetes*: 0 (excluded) • *Percentage with uveitis*: 0 (excluded) **Comparator: Steroids plus placebo** • *Number of people (eyes) randomised*: 49 (49) • *Number (%) of people followed up*: 44 (90) • *Average age in years*: 66

	• *Age range in years*: NR • *Percentage women*: 50 • *Ethnic group*: NR • *Percentage with diabetes*: 0 (excluded) • *Percentage with uveitis*: 0 (excluded) **Included criteria:** Nuclear cataract density of 2 and 3 determined by LOCS II; (> 50 years old); indication for cataract surgery with IOL implantation under local anaesthesia **Excluded criteria:** Diabetes; NSAID use; use of topical eye drops (including antiglaucoma drugs); uveitis; macular disease; pseudoexfoliation syndrome; congenital ocular abnormalities; cataract density of 1 and 4 determined by LOCS II; previous intraocular surgery; previous injections; complications during cataract surgery (e.g. posterior capsule rupture, vitreous loss, retained cortical material, or an IOL not placed in the capsular bag); not follow instructions or if they did not show up for appointments **Pretreatment:** No major imbalances in age, gender and visual acuity. **Eyes:** Probably one eye only included in the trial but not clearly reported and unclear how selected

Interventions	**Intervention: NSAIDs plus steroids**
	• ketorolac tromethamine 0.4% (Acular LS, Allergan, Inc)
	  ○ *Times per day*: 4 times
	  ○ *Duration preoperative: days*: 3
	  ○ *Duration postoperative: days*: 35
	• prednisolone acetate 1% (Pred Forte; Allergan,Inc)
	  ○ *Times per day*: 4 times
	  ○ *Duration preoperative: days*: 3
	  ○ *Duration postoperative: days*: 35
	Comparator: Steroids plus placebo
	• prednisolone acetate 1% (Pred Forte; Allergan,Inc)
	  ○ *Times per day*: 4 times
	  ○ *Duration preoperative: days*: 3
	  ○ *Duration postoperative: days*: 35
	• placebo (dextran 70/hypromellose, Lacribell, Latinofarma;Industrias Farmaceuticas Ltda)
	  ○ *Times per day*: 4 times
	  ○ *Duration preoperative: days*: 3
	  ○ *Duration postoperative: days*: 35
	Type of surgery: Phacoemulsification

Outcomes	**Follow-up:** 5 weeks • CRT at follow-up (final value) • Adverse effects • CMO (fluorescein angiography using Miyake 1977 classification) • BCVA logMAR (final value)
Contact details	**Authors name:** Dr. Flavia G. Ticly **Institution:** Department of Ophthalmology, University of Campinas (UNICAMP), Campinas, Sao Paulo, Brazil **Email:** flaviaticly@gmail.com **Address:** Department of OphthalmologyUniversity of Campinas (UNICAMP)P.O. Box

Ticly 2014 (*Continued*)

	6111Campinas 13083-970, Sao Paulo, Brazil
Notes	**Funding sources:** NR **Declaration of interest:** Reported no competing financial interests exist. **Date study conducted:** February 2011 to March 2012 **Trial registration number:** NTC01542190 **Contacting study investigators:** Trial authors not contacted.

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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Judgement comment: Each of the 2 intervention groups received 50 different numbers from a random number table. These numbers were transferred to small individual envelopes and also affixed to one of the relabeled eye drop bottles. Unclear how this would work
Allocation concealment (selection bias)	Unclear risk	Judgement comment: Numbers were transferred to small individual envelopes and also affixed to one of the relabeled eye drop bottles. Unclear how this concealed the allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement comment: Placebo-controlled study. We assume the masking was effective
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: Placebo-controlled study. We assume the masking was effective. It was stated that the surgeon and the ophthalmologist who collected the data were not aware of the group assignment of the patients
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: 89% follow-up. Five patients (10%) did not complete the trial in the placebo group while five patients (11%) did not complete the study in the ketorolac group
Selective reporting (reporting bias)	Unclear risk	Judgement comment: No access to protocol or trial registry entry

Tunc 1999

Methods	**Study design:** Parallel group RCT
Participants	**Country:** Turkey **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: 50 (50) • *Number (%) of people followed up*: 50 (100%) • *Average age in years*: 61 • *Age range in years*: NR • *Percentage women*: 38% • *Ethnic group*: NR • *Percentage with diabetes*: 0 (excluded) • *Percentage with uveitis*: 0 (excluded) **Comparator: Steroids alone** • *Number of people (eyes) randomised*: 25 (25) • *Number (%) of people followed up*: 25 (100%) • *Average age in years*: 65 • *Age range in years*: NR • *Percentage women*: 40% • *Ethnic group*: NR • *Percentage with diabetes*: 0 (excluded) • *Percentage with uveitis*: 0 (excluded) **Inclusion criteria:** Patients with unilateral cataracts. **Exclusion criteria:** Diabetes; rheumatoid disease; immunological disease; uveitis; glaucoma; ARMD; retinitis pigmentosa; retinal detachment; NSAIDs use; corticosteroid use; diuretic use; antihistaminics; previous eye surgery; surgical complications (e.g.. posterior capsular tear, vitreous loss, iatrogenic iridodialysis); combined surgery; postoperative complications (e.g.. iris capture, retinal detachment, choroidal detachment); noncompliance with medications; use of systemic steroids or NSAIDs during the follow-up period; definite posterior capsule opacification **Pretreatment:** No differences in age sex, and hypertension. **Eyes:** One eye, people with unilateral cataracts recruited.

Interventions	**Intervention: NSAIDs plus steroids**
	• diclofenac sodium 0.1% (brand name not reported)
	  ◦ *Times per day*: 4 times
	  ◦ *Duration preoperative: days*: 1
	  ◦ *Duration postoperative: days*: 56
	• dexamethasone sodium phosphate 1% (brand name not reported)
	  ◦ T*imes per day*: 4 times a day for 21 days; 3 times a day from day 22 to 56
	  ◦ *Duration preoperative: days*: 0
	  ◦ *Duration postoperative: days*: 56
	Comparator: Steroids alone
	• dexamethasone sodium 1% (brand name not reported)
	• *Times per day*: 4 times a day for 21 days, 3 times a day from day 22 to 56
	• *Duration preoperative: days*: 0
	• *Duration postoperative: days*: 56
	At the end of surgery all participants had subconjunctival injection of dexamethasone and gentamicin. All participants used 0.03% tobramycin eye drops postoperatively 4

Tunc 1999 (*Continued*)

	times a day for 14 days **Type of surgery:** ECCE
Outcomes	**Follow-up:** 2 months • CMO (fluorescein angiography 0 no leakage (CME absent),1 oedema less than perifoveal, 2 mild perifoveal oedema, 3 moderate perifoveal oedema (approx 1 disc diameter), 4 severe perifoveal oedema plus drop of 1 line of Snellen acuity since second postoperative week defined as "clinically significant")
Contact details	**Authors name:** Murat Tunc **Institution:** Dokuz Eylul University Medical School **Email:** NR **Address:** Dokuz Eylul University Cumhuriyet Blv No:144, 35210 Alsancak/i zmir, Turkey
Notes	**Funding sources:** NR **Declaration of interest**: NR **Date study conducted:** NR **Trial registration number:** NR **Contacting study investigators:** Trial authors not contacted.

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: Not reported how list was generated. Trial was described as "randomised" but with no further details
Allocation concealment (selection bias)	Unclear risk	Judgement comment: Not reported how allocation administered. Trial was described as "randomised" but with no further details
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information on masking. We assume that in absence of reporting on this participants and personnel were not masked
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The angiograms were read by the retina unit (Dr Saatchi); the patients' names and treatment protocols were kept hidden Judgement quote: No other information on other outcomes.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement Comment: Follow-up not reported.
Selective reporting (reporting bias)	Unclear risk	Judgement Comment: No access to protocol or trial registry entry

Tzelikis 2015

Methods	**Study design:** Parallel group RCT
Participants	**Country:** Brazil **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: not reported by group • *Number (%) of people followed up*: 45 (45 eyes) • *Average age in years*: 65 (reported for whole cohort only) • *Age range in years*: 50 to 90 (reported for whole cohort only) • *Percentage women*: 56% (reported for whole cohort only) • *Ethnic group*: NR • *Percentage with diabetes*: NR • *Percentage with uveitis*: NR **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: not reported by group • *Number (%) of people followed up*: 41 (41 eyes) • *Average age in years*: 65 (reported for whole cohort only) • *Age range in years*: 50 to 90 (reported for whole cohort only) • *Percentage women*: 56% (reported for whole cohort only) • *Ethnic group*: NR • *Percentage with diabetes*: NR • *Percentage with uveitis*: NR **Comparator: Steroids plus placebo** • *Number of people (eyes) randomised*: not reported by group • *Number (%) of people followed up*: 40 (40 eyes) • *Average age in years*: 65 (reported for whole cohort only) • *Age range in years*: 50 to 90 (reported for whole cohort only) • *Percentage women*: 56% (reported for whole cohort only) • *Ethnic group*: NR • *Percentage with diabetes*: NR • *Percentage with uveitis*: NR **Inclusion criteria:** Older than 40 years; age-related cataract; normal ophthalmological exam **Exclusion criteria:** Previous ocular surgery; central endothelial cell count < 2000 cells/mm2; glaucoma or IOP > 21 mmHg; amblyopia; retinal abnormalities; steroid or immunosuppressive treatment; connective tissue diseases; allergy or hypersensitivity to NSAIDs; enrolled patients with complicated cataract surgery (e.g. posterior capsule rupture, vitreous loss or an IOL not placed in the capsular bag) **Pretreatment:** Group differences at baseline not reported. **Eyes:** One eye, unclear how selected.

Interventions	**Intervention: NSAIDs plus steroids**
	• ketorolac tromethamine 0.4% (Acular LS, Allergan)
	  ○ *Times per day*: 4 times
	  ○ *Duration preoperative: days*: 2
	  ○ *Duration postoperative: days*: 28
	• prednisolone 1% (brand name not reported)
	  ○ *Times per day*: 4 times a day for 7 days, 3 times a day for 7 days, twice a day for 7 days, once a day for 7 days
	  ○ *Duration preoperative: days*: 0

	○ *Duration postoperative: days*: 28 **Intervention: NSAIDs plus steroids** • nepafenac 0.1% (Nevanec, Alcon) ○ *Times per day*: 3 times ○ *Duration preoperative: days*: 2 ○ *Duration postoperative: days*: 28 • prednisolone 1% (brand name not reported) ○ *Times per day*: 4 times a day for 7 days, 3 times a day for 7 days, twice a day for 7 days, once a day for 7 days ○ *Duration preoperative: days*: 2 ○ *Duration postoperative: days*: 28 **Comparator: Steroids plus placebo** • prednisolone 1% (brand name not reported) ○ *Times per day*: 4 times a day for 7 days, 3 times a day for 7 days, twice a day for 7 days, once a day for 7 days ○ *Duration preoperative: days*: 2 ○ *Duration postoperative: days*: 28 • placebo (artificial tears) ○ *Times per day*: 4 times ○ *Duration preoperative: days*: 2 ○ *Duration postoperative: days*: 28 All participants received moxifloxacin 0.5% 4 times a day 2 days before surgery and 7 days postoperatively **Type of surgery:** Phacoemulsification
Outcomes	**Follow-up:** 12 weeks for some outcomes, 30 days for others • CRT at follow-up (final value) • Adverse effects • BCVA logMAR (final value)
Contact details	**Authors name:** Patrick F Tzelikis **Institution:** Brasilia Ophthalmologic Hospital **Email:** tzelikis@gmail.com **Address:** Brasilia Ophthalmologic Hospital, HOB, SQN 203, bloco K, apart 502, Brasilia, DF 70833-110, Brazil
Notes	**Funding sources:** NR **Declaration of interest:** Reported no competing interests **Date study conducted:** June 2013 to October 2013 **Trial registration number:** NCT02084576. **Contacting study investigators:** Trial authors not contacted.

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were assigned in a 1:1:1 ratio to one of three treatment groups using a computer-generated randomisation list."

Tzelikis 2015 (*Continued*)

Allocation concealment (selection bias)	Low risk	Quote: "All investigators were masked with regard to treatment group."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement comment: Placebo-controlled.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All investigators were masked with regard to treatment group." Judgement comment: Placebo-controlled.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Follow-up by intervention group not reported.
Selective reporting (reporting bias)	Unclear risk	Judgement comment: Trial study protocol registered at NCT02084576 but does not clearly define outcomes

Umer-Bloch 1983

Methods	**Study design:** Parallel group RCT
Participants	**Country:** Switzerland **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: NR • *Number (%) of people followed up*: 35 (NR) • *Average age in years*: 68 • *Age range in years*: NR • *Percentage women*: 51% • *Ethnic group*: NR • *Percentage with diabetes*: NR (but people with diabetic retinopathy were excluded) • *Percentage with uveitis*: 0 (excluded) **Comparator: Steroids plus placebo** • *Number of people (eyes) randomised*: NR • *Number (%) of people followed up*: 38 (NR) • *Average age in years*: 70 • *Age range in years*: NR • *Percentage women*: 53% • *Ethnic group*: NR • *Percentage with diabetes*: NR (but people with diabetic retinopathy were excluded) • *Percentage with uveitis*: 0 (excluded) **Included criteria:** Intracapsular cataract extraction (124 persons); 40 patients with IOL implantation after cataract extraction **Excluded criteria:** Maculopathy; diabetic retinopathy; prior uveitis; systemic steroid therapy **Pretreatment:** Unclear if groups comparable. **Eyes:** Unclear if one or both eyes included.

Umer-Bloch 1983 (*Continued*)

Interventions	**Intervention: NSAIDs plus steroids** • indomethacin 1% (Indoptic, Merck, Sharp and Dohme-Chibret) ○ T*imes per day*: 4 times ○ *Duration preoperative: days*: 1 ○ *Duration postoperative: days*: 84 **Comparator: Steroids plus placebo** • dexamethasone (combined with either chloramphenicol (Spersadex) or neomycin (Maxitrol)) ○ *Times per day*: NR ○ *Duration preoperative: days*: NR ○ *Duration postoperative: days*: NR • placebo (vehicle) ○ *Times per day*: 4 times ○ *Duration preoperative: days*: 1 ○ *Duration postoperative: days*: 84 Additional for all participants: cycloplegics (atropine 1%); if necessary timoptic or diamox to lower eye pressure **Type of surgery:** ECCE (40) ICCE (124)
Outcomes	**Follow-up:** 12 weeks • Adverse effects • CMO (fluorescein angiography using Miyake 1977 classification) • BCVA (Snellen only, not included in the analyses)
Contact details	**Authors name:** U Umer-Bloch **Institution:** University Augenklink Zurich **Email:** NR **Address:** University Augenklinik, Ramistrasse 100, CH-8091 Zurich
Notes	**Funding sources:** NR **Declaration of interest**: NR **Date study conducted:** NR **Trial registration number:** NR **Contacting study investigators:** Trial authors not contacted.

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: Not reported how list was generated. Trial was described as "randomised" but with no further details
Allocation concealment (selection bias)	Unclear risk	Judgement comment: Not reported how allocation was administered. Trial was described as "randomised" but with no further details

Umer-Bloch 1983 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement comment: Medication placed by nurses in a bottle with suspension: one with indomethacin another with vehicle. Neither the examiner nor the patient knew the contents of the bottle
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: Placebo-controlled using vehicle only. Patients, nurses, physician analysing fluorescein angiography were masked
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: For 35 patients the study was stopped before the end of the study because of intra-operative complications or they had, as only later recognized, an exclusion criteria as defined as maculopathy, diabetic retinopathy, prior uveitis or a systemic steroid therapy. Not reported to which groups these patients belonged
Selective reporting (reporting bias)	Unclear risk	Judgement comment: No access to protocol or trial registry entry

Wang 2013

Methods	**Study design:** Parallel group RCT **Open label**
Participants	**Country:** China **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: 120 (NR) • *Number (%) of people followed up*: 83 (69%) • *Average age in years*: 73 (reported for whole cohort only) • *Age range in years*: 46-92 (reported for whole cohort only) • *Percentage women*: 54% (reported for whole cohort only) • *Ethnic group*: 100% Han Chinese • *Percentage with diabetes*: 0 (excluded) • *Percentage with uveitis*: 0 (excluded) **Comparator: Steroids alone** • *Number of people (eyes) randomised*: 120 (NR) • *Number (%) of people followed up*: 84 (70%) • *Average age in years*: 73 (reported for whole cohort only) • *Age range in years*: 46-92 (reported for whole cohort only) • *Percentage women*: 54% (reported for whole cohort only) • *Ethnic group*: 100% Han Chinese • *Percentage with diabetes*: 0 (excluded) • *Percentage with uveitis*: 0 (excluded) **Inclusion criteria:** Age-related cataract patients undergoing phacoemulsification with

	posterior chamber IOL implantation **Exclusion criteria:** Any ocular diseases that might affect treatment responses or evaluations, such as corneal disease, glaucoma, uveitis, retinal detachment, optic neuropathy or amblyopia; any systemic diseases that might affect treatment responses or evaluations, such as diabetes mellitus; potentially pregnant women; systemic or topical anti-inflammatory therapy within 1 month prior to surgery and contraindication of oral steroids, such as patients with peptic ulcer, cancer and tuberculosis; surgical complications, such as posterior capsule rupture or hyphema; special diseases which might affect surgery in the eyes, such as limitation of pupil dilation **Pretreatment:** Groups were not compared. **Eyes:** Not clearly reported but probably one eye per person, unclear how selected
Interventions	**Intervention: NSAIDs plus (oral) steroids** • bromfenac sodium 0.1% (brand name not reported, Senju Pharmaceutical Co., Ltd) ○ *Times per day*: twice a day ○ *Duration preoperative: days*: 0 ○ *Duration postoperative: days*: 30 and 60 • prednisolone 15 mg PO (brand name not reported) ○ *Times per day*: once ○ *Duration preoperative: days*: 0 ○ *Duration postoperative: days*: 7 **Comparator: Steroids alone** • fluorometholone 0.1% and dexamethasone 0.1% (brand name not reported, Santen Pharmaceutical Co. Ltd. and Wujing Pharmaceutical Co. Ltd) ○ *Times per day*: 3 times ○ *Duration preoperative: days*: 0 ○ *Duration postoperative: days*: 30 • prednisolone 15mg PO (brand name not reported) ○ *Times per day*: once ○ *Duration preoperative: days*: 0 ○ *Duration postoperative: days*: 7 All participants received levofloxacin eye drops (Santen PharmaceuticalCo., Ltd) 4 times a day for 1 day preoperatively and 7 days postoperatively. **Type of surgery:** Phacoemulsification
Outcomes	**Follow-up:** 2 months • Poor vision outcome due to MO (unclear what vision cutpoint used) • CRT at follow-up (final value) • Adverse effects • CMO (Quote "CME was defined as central retinal thickness > 250 μm and the presence of intraretinal cystoid space • beneath the foveal, with the diagnosis confirmed by the same retinal specialist.") • Inflammation (mean photon count values) • BCVA logMAR

Wang 2013 (*Continued*)

Contact details	**Authors name:** Ke Yao **Institution:** Medical College of Zhejiang University **Email:** xlren@zju.edu.cn **Address:** Eye Center, 2nd Affiliated Hospital Medical College of Zhejiang University Hangzhou 310009 (China)
Notes	**Funding sources:** "This study was supported by grants from Zhejiang Key Innovation Team Project of China (grant no. 009R50039) and Zhejiang Key Laboratory Fund of China (No.2011E10006)." **Declaration of interest:** NR **Date study conducted:** October 2010 to December 2011 **Trial registration number:** NR **Contacting study investigators:** Trial authors not contacted

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were randomly and prospectively assigned into four groups (OBS1, OBS2, OFM and ODM) by a random-numbers table."
Allocation concealment (selection bias)	High risk	Judgement comment: The drugs were applied topically to the assigned patients open-label. The same physician served as the medical monitor and assigned one of the drugs to each patient
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: The drugs were applied topically to the assigned patients open-label. The same physician served as the medical monitor and assigned one of the drugs to each patient
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: The drugs were applied topically to the assigned patients open-label. The same physician served as the medical monitor and assigned one of the drugs to each patient
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: Follow-up was 83/120 (69%) in NSAIDs group and 84/120 (70%) in the steroid group. Significant loss to follow-up but similar in both groups
Selective reporting (reporting bias)	Unclear risk	Judgement comment: No access to protocol or trial registry entry

Wittpenn 2008

Methods	**Study design:** Parallel group RCT
Participants	**Country:** USA **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: 268 (268) • *Number (%) of people followed up*: 227 (85%) given OCT at 4 weeks; 35 (13%) at 6 weeks • *Average age in years*: 70 • *Age range in years*: NR • *Percentage women*: 53% (only reported for whole cohort) • *Ethnic group*: 82% white (only reported for whole cohort) • *Percentage with diabetes*: NR • *Percentage with uveitis*: NR **Comparator: Steroids plus placebo** • *Number of people (eyes) randomised*: 278 (278) • *Number (%) of people followed up*: 251 (90%) given OCT at 4 weeks; 42 (15%) at 6 weeks • *Average age in years*: 70 • *Age range in years*: NR • *Percentage women*: 53% (only reported for whole cohort) • *Ethnic group*: 82% white (only reported for whole cohort) • *Percentage with diabetes*: NR • *Percentage with uveitis*: NR **Inclusion criteria:** Scheduled to undergo cataract surgery; 20/20 BCVA potential without any evidence of macular abnormality, including age-related macular changes, epiretinal membranes, or other retinal-vascular anomalies **Exclusion criteria:** Systemic diseases with ocular manifestations of the disease (e.g. diabetic patients with normal retinal exams were not excluded); vitreous loss or capsular disruption/rupture occurred during surgery; postoperative day 1, the surgeon felt the amount of inflammation was greater than expected and, in his best clinical judgment, more aggressive anti-inflammatory treatment was indicated **Pretreatment:** Quote: "There were no statistically significant between-group differences in any demographic variable." But no data reported **Eyes:** One eye, unclear how selected.
Interventions	**Intervention: NSAIDs plus steroids** • ketorolac 0.4% (Acular LS, Allergan Inc, Irvine, California, USA) ◦ *Times per day*: 4 times a day , 4 doses every 15 minutes one hour preoperative ◦ *Duration preoperative: days*: 3 ◦ *Duration postoperative: days*: 28 to 42 • prednisolone acetate 1% (Pred Forte, Allergan Inc) ◦ *Times per day*: 4 times ◦ *Duration preoperative: days*: 0 ◦ *Duration postoperative: days*: "until one 5 ml bottle was empty" **Comparator: Steroids plus placebo** • prednisolone acetate 1% (Pred Forte, Allergan Inc) ◦ *Times per day*: 4 times ◦ *Duration preoperative: days*: 0

	○ *Duration postoperative: days*: "until they exited the study" • placebo (artificial tears) ○ *Brand name*: NR ○ *Times per day*: 4 times ○ *Duration preoperative: days*: 3 ○ *Duration postoperative: days*: "until one 5 ml bottle was empty" The comparator group: "...also received four drops of ketorolac 0.4% one hour prior to cataract surgery." **Type of surgery:** Phacoemulsification
Outcomes	**Follow-up:** 4 weeks • Poor vision outcome due to MO (OCT-confirmed CMO with visual acuity < 6/9.) • Adverse effects • CMO (Quote: "Definite CME: Presence of cystoid changes associated with substantial (> 40μm) retinal thickening evident on OCT. 2. Probable CME: Presence of changes in retinal contour and increased macular thickness relative to preoperative baseline, but without definite cystoid changes. 3. Possible CME: Mild to moderate changes in retinal thickness or contour without cystoid changes")
Contact details	**Authors name:** John R. Wittpenn **Institution:** State University of New York at Stony Brook **Email:** jrwittpenn@aol.com **Address:** State University of New York at Stony Brook, 2500 Route 347, Building 24, Stony Brook, NY 11790
Notes	**Funding sources:** "This study was supported by an unrestricted education grant from Allergan Inc, Irvine, Calfiornia." **Declaration of interest:** "The authors indicate no financial conflict of interest." **Date study conducted:** June 2005 to August 2006 **Trial registration number:** NCT00348244 **Contacting study investigators:** Trial authors not contacted.

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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised in a 1:1 ratio using a randomly generated list of patient identification numbers."
Allocation concealment (selection bias)	Low risk	Quote: "A central coordination center (IMEDS Inc, Riverside, California, USA; [M.E.]) generated the allocation sequence, enrolled participants, and assigned participants to their treatment groups."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The patients and technical staff were unmasked because regulations prevented the medications from being repackaged into similar, un-

Wittpenn 2008 (*Continued*)

		marked bottles. The labels were covered but the technicians were capable of recognizing the bottle color and shape. Patients, however, would only have been unmasked if they researched the type and shape of the different bottles."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All investigators were masked with regard to treatment group."
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: Very low follow-up at 6 weeks. "Of the 546 patients who entered the study, 77 patients also returned for the week-6 visit, 35 in the ketorolac/steroid group and 42 in the steroid group."
Selective reporting (reporting bias)	Unclear risk	Judgement comment: No access to protocol and trial registry entry did not include outcomes

Yannuzzi 1981

Methods	**Study design:** Parallel group RCT
Participants	**Country:** USA **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: NR (100) • *Number (%) of people followed up*: 59 eyes (59%) • *Average age in years*: NR • *Age range in years*: NR • *Percentage women*: NR • *Ethnic group*: NR • *Percentage with diabetes*: NR • *Percentage with uveitis*: NR **Comparator: Steroids plus placebo** • *Number of people (eyes) randomised*: NR (131) • *Number (%) of people followed up*: 77 eyes (59%) • *Average age in years*: NR • *Age range in years*: NR • *Percentage women*: NR • *Ethnic group*: NR • *Percentage with diabetes*: NR • *Percentage with uveitis*: NR **Included criteria:** Patients undergoing intracapsular cataract extraction. **Excluded criteria:** Undergone procedures other than conventional ICCE; pre-existing macular disease predisposing to macular oedema, such as neovascular age-related macular degeneration **Pretreatment:** Baseline comparisons not reported.

	Eyes: 21 people had bilateral cataract surgery - the second eye was randomised separately

Interventions	**Intervention: NSAIDs plus steroids**
	• indomethacin 1% (brand name not reported, Merck Sharp & Dohme)
	  ○ *Times per day*: Three drops prior to surgery and 4 times a day after
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days*: 28-42
	• steroids given as part of standard care, not specified exactly what
	Comparator: Steroids plus placebo
	• steroids given as part of standard care, not specified exactly what
	• placebo (vehicle)
	  ○ *Times per day*: Three drops prior to surgery and 4 times a day after
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days*: 28-42
	Quote: "Routine postoperative drops such as cycloplegics, antibiotics and steroids were also given as was the custom of the operating ophthalmologist."
	Type of surgery: ICCE

Outcomes	**Follow-up:** 1 year • Poor vision outcome due to MO (BCVA 6/60 or worse) • Adverse effects • CMO (fluorescein angiography, CMO not defined, reported at 5 and 10 weeks)
Contact details	**Authors name:** Lawrence A Yannuzzi **Institution:** Manhattan Eye, Ear and Throat Hospital **Email:** NR **Address:** Manhattan Eye, Ear and Throat Hospital 210 E 64th St, New York, NY 10021, United States
Notes	**Funding sources:** LuEster Mertz Retinal Research Fund of the Eye, Ear and Throat Hospital **Declaration of interest**: NR **Date study conducted:** NR **Trial registration number:** NR **Contacting study investigators:** Trial authors not contacted.

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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Judgement comment: Not reported how list was generated. Allocation was described as being done "in a random fashion" but with no further details
Allocation concealment (selection bias)	High risk	Judgement comment: Pharmacist involved in giving treatment did not appear to be masked to treatment

Yannuzzi 1981 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement comment: Placebo-controlled study described as "double-masked"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Judgement comment: Placebo-controlled study described as "double-masked"
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: Follow-up 59% in both groups. High loss to follow-up at 1 year 38/100 (38%) in NSAIDs group and 50/131 (38%) in the control group
Selective reporting (reporting bias)	Unclear risk	Judgement comment: No access to protocol or trial registry entry

Yavas 2007

Methods	**Study design:** Parallel group RCT
Participants	**Country:** Turkey **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: 126 (126) • *Number (%) of people followed up*: 121 (96%) • *Average age in years*: 64 • *Age range in years*: NR • *Percentage women*: 43% • *Ethnic group*: NR • *Percentage with diabetes*: 0 (excluded) • *Percentage with uveitis*: 0 (excluded) **Comparator: Steroids alone** • *Number of people (eyes) randomised*: 63 (63) • *Number (%) of people followed up*: 58 (92%) • *Average age in years*: 65 • *Age range in years*: NR • *Percentage women*: 36% • *Ethnic group*: NR • *Percentage with diabetes*: 0 (excluded) • *Percentage with uveitis*: 0 (excluded) **Inclusion criteria:** NR **Exclusion criteria:** History of intraocular surgery; any complication during cataract surgery; glaucoma; uveitis; vitreoretinal pathology; history of diabetes mellitus, hypertension, or cardiac disease; or topical or systemic drug use **Pretreatment:** Some imbalances in age and sex but unclear if important. **Eyes:** Right eye only included.

Yavas 2007 (*Continued*)

Interventions	**Intervention:** NSAIDs**plus steroids** • indomethacin 0.1% (brand name not reported) ○ *Times per day*: 4 times a day preoperative; 3 times a day postoperative. Half received postoperatively only. ○ *Duration preoperative: days*: 3 ○ *Duration postoperative: days*: 30 • prednisolone acetate 1% (brand name not reported) ○ *Times per day*: 4 times ○ *Duration preoperative: days*: 0 ○ *Duration postoperative: days*: 30 **Comparator: Steroids alone** • prednisolone acetate 1% (brand name not reported) ○ *Times per day*: 4 times ○ *Duration preoperative: days*: 0 ○ *Duration postoperative: days*: 30 All participants received 1 drop of topical antibiotic (ofloxacin 0.3%) 4 times a day daily for 1 week **Type of surgery:** Phacoemulsification
Outcomes	**Follow-up:** 3 months • CMO (Quote: "Slight fluorescein leakage into the cystic space without enclosing the entire central fovea or complete fluorescein accumulation in the cystic space was diagnosed as angiographic CME." • BCVA (final value)
Contact details	**Authors name:** Guliz Yavas **Institution:** Afyon Kocatepe University **Email:** gkumbar@ttnet.net.tr **Address:** P.K. 25, 06502 Bahcelievler, Ankara, Turkey
Notes	**Funding sources:** NR **Declaration of interest:** "No author has a financial or proprietary interest in any material or method mentioned." **Date study conducted:** NR **Trial registration number:** NR **Contacting study investigators:** Trial authors not contacted.

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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised into 3 groups." Judgement comment: Not reported how list was generated. Trial was described as "randomised" but with no further details
Allocation concealment (selection bias)	Unclear risk	Judgement comment: Not reported how allocation administered. Trial was described as "randomised"

Yavas 2007 (*Continued*)

		but with no further details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: No information on masking. We assume that in absence of reporting on this patients and personnel were not masked
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Fluorescein angiography was performed in all patients, and fluorescein leakage to diagnose angiographic CME was evaluated by a masked observer." Judgement comment: Unclear if other outcomes were masked.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: Follow-up not reported.
Selective reporting (reporting bias)	Unclear risk	Judgement comment: No access to protocol or trial registry entry

Yung 2007

Methods	**Study design:** Parallel group RCT
Participants	**Country:** USA **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: 19 (NR) • *Number (%) of people followed up*: NR • *Average age in years*: NR • *Age range in years*: NR • *Percentage women*: NR • *Ethnic group*: NR • *Percentage with diabetes*: 100% • *Percentage with uveitis*: NR **Comparator: Steroids plus placebo** • *Number of people (eyes) randomised*: 18 (NR) • *Number (%) of people followed up*: NR • *Average age in years*: NR • *Age range in years*: NR • *Percentage women*: NR • *Ethnic group*: NR • *Percentage with diabetes*: 100% • *Percentage with uveitis*: NR **Inclusion criteria:** Diabetic patients having cataract surgery. **Exclusion criteria:** NR **Pretreatment:** Group differences not reported. **Eyes:** Unclear if one or both eyes included.

Interventions	**Intervention: NSAIDs plus steroids**
	• ketorolac 0.5% (brand name not reported)
	  ○ *Times per day*: NR
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days*: 28
	• steroid (not specified)
	  ○ *Times per day*: NR
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days*: 28
	Comparator: Steroids plus placebo
	• steroid (not specified)
	  ○ *Times per day*: NR
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days*: 28
	• placebo (not specified)
	  ○ *Times per day*: NR
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days*: 28
	Type of surgery: NR

Outcomes	**Follow-up:** 12 weeks • Change in CRT (reported statistical significance only, no data)
Contact details	**Authors name:** C Yung **Institution:** Indiana University **Email:** NR **Address:** Indiana University107 S Indiana Ave, Bloomington, IN 47405, United States
Notes	**Funding sources:** NR **Declaration of interest:** NR **Date study conducted:** NR **Trial registration number:** NR **Contacting study investigators:** Abstract only, tried to contact authors but could not find email address

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: Not reported how list was generated. Trial was described as "randomised" but with no further details
Allocation concealment (selection bias)	Unclear risk	Judgement comment: Not reported how allocation administered. Trial was described as "randomised" but with no further details

Yung 2007 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Judgement comment: Placebo-controlled but no information on who was masked
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Judgement comment: Placebo-controlled but no information on who was masked
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: Follow-up not reported.
Selective reporting (reporting bias)	Unclear risk	Judgement comment: No access to protocol or trial registry entry

Zaczek 2014

Methods	**Study design:** Parallel group RCT
Participants	**Country:** Sweden **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: 80 (80) • *Number (%) of people followed up*: 75 (94%) • *Average age in years*: 70 • *Age range in years*: NR • *Percentage women*: 64% • *Ethnic group*: NR • *Percentage with diabetes*: NR • *Percentage with uveitis*: NR **Comparator: Steroids plus placebo** • *Number of people (eyes) randomised*: 80 (80) • *Number (%) of people followed up*: 77 (96%) • *Average age in years*: 68 • *Age range in years*: NR • *Percentage women*: 65% • *Ethnic group*: NR • *Percentage with diabetes*: NR • *Percentage with uveitis*: NR **Inclusion criteria:** 45 and 85 years of age; cataract surgery under local anaesthesia; translucent cataract for good-quality OCT scans of the macular at baseline **Exclusion criteria:** Small pupils (< 5.0 mm after pharmacologic dilation); dark brown irides; exfoliation syndrome, history of uveitis; glaucoma; macular degeneration; vision impairing eye disorder except cataract; diabetic patients; pregnant women; patients using topical or systemic anti-inflammatory treatment; hypersensitivity to any of the given study treatments; intraoperative difficulties (e.g. loose zonular fibres, extended operating time, residual cortical material); intraoperative complications (e.g. posterior capsule rupture and vitreous loss) **Pretreatment:** No major imbalances, age, gener and operated eye compared.

	Eyes: One eye, unclear how selected.

Interventions	**Intervention: NSAIDs plus steroids**
	• nepafenac 0.1% (brand name not reported)
	  ○ *Times per day*: 3 times
	  ○ *Duration preoperative: days*: 2
	  ○ *Duration postoperative: days*: 21
	• dexamethasone 0.1% (Isopto-Maxidex)
	  ○ *Times per day*: 3 times
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days*: 21
	Comparator: Steroids plus placebo
	• dexamethasone 0.1% (Isopto-Maxidex)
	  ○ *Times per day*: 3 times
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days*: 21
	• placebo (Tears Naturale II Polyquad)
	  ○ *Times per day*: thrice before surgery 5 minutes apart/3 times a day
	  ○ *Duration preoperative: days*: 2
	  ○ *Duration postoperative: days*: 21
	Type of surgery: Phacoemulsification

Outcomes	**Follow-up:** 6 weeks • Adverse effects • CMO (OCT-verified but not defined) • Inflammation (mean anterior chamber reported in figure but no SD could be calculated) • BCVA logMAR (final value) • Change in total macular volume
Contact details	**Authors name:** Anna Zaczek **Institution:** Scanloc Healthcare AB **Email:** anna. zaczek@scanloc.se **Address:** Scanloc Healthcare AB, Lilla Bommen 6, 411 04 Gothenburg, Sweden
Notes	**Funding sources:** Supported by Alcon Research Ltd, Fort Worth, Texas, USA, and S. A. Alcon-Couvreur N.V. Puurs, Belgium, which produced and provided the masked eyedrop bottles. Partially supported by Alcon, Inc. Sweden. Financial support was also provided through the regional agreement on Medical training and Clinical research (ALF) between Stockholm County Council and Karolinska Institutet (20120623) **Declaration of interest:** "No author has a financial or proprietary interest in any material or method mentioned." **Date study conducted:** NR **Trial registration number:** NR **Contacting study investigators:** Trial authors not contacted.

Risk of bias			***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**	

Zaczek 2014 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Judgement comment: Not reported how list was generated. Trial described as "randomised" but with no further details
Allocation concealment (selection bias)	Low risk	Quote: "All products used in this clinical trial were produced, labelled, packaged, and released by S.A. Alcon-Couvreur N.V. Puurs, Belgium. Nepafenac and placebo suspensions were supplied in identical bottles labelled with a protocol and a patient number so neither the investigators nor the patients were able to identify their contents."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All products used in this clinical trial were produced, labelled, packaged, and released by S.A. Alcon-Couvreur N.V. Puurs, Belgium. Nepafenac and placebo suspensions were supplied in identical bottles labelled with a protocol and a patient number so neither the investigators nor the patients were able to identify their contents."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All products used in this clinical trial were produced, labelled, packaged, and released by S.A. Alcon-Couvreur N.V. Puurs, Belgium. Nepafenac and placebo suspensions were supplied in identical bottles labelled with a protocol and a patient number so neither the investigators nor the patients were able to identify their contents"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: Missing data less than 20% (i.e. more than 80% follow-up) and equal follow-up in both groups and no obvious reason why loss to follow-up should be related to outcome
Selective reporting (reporting bias)	Unclear risk	Judgement comment: No access to protocol or trial registry entry

Zhang 2008

Methods	**Study design:** Parallel group RCT
Participants	**Country:** China **Setting:** Eye hospital **Intervention: NSAIDs plus steroids** • *Number of people (eyes) randomised*: NR (110) • *Number (%) of people followed up*: 110 eyes (100%) • *Average age in years*: NR • *Age range in years*: 55-87 (reported for whole cohort only) • *Percentage women*: 55% (reported for whole cohort only)

	• *Ethnic group*: NR • *Percentage with diabetes*: NR • *Percentage with uveitis*: NR **Comparator: Steroids alone** • *Number of people (eyes) randomised*: NR (110) • *Number (%) of people followed up*: 110 eyes (100%) • *Average age in years*: NR • *Age range in years*: 55-87 (reported for whole cohort only) • *Percentage women*: 55% (reported for whole cohort only) • *Ethnic group*: NR • *Percentage with diabetes*: NR • *Percentage with uveitis*: NR **Included criteria:** NR **Excluded criteria:** NR **Pretreatment:** No information on pretreatment differences. **Eyes:** 220 eyes of 198 people.

Interventions	**Intervention: NSAIDs plus steroids**
	• pranoprofen (brand name not reported)
	  ○ *Times per day*: NR
	  ○ *Duration preoperative: days*: NR
	  ○ *Duration postoperative: days*: 28
	• dexamethasone (combined with tobramycin)
	  ○ *Times per day*: 4 times a day for 2 weeks 3 times a day for 2 weeks
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days*: 28
	Comparator: Steroids alone
	• dexamethasone (combined with tobramycin)
	  ○ *Times per day*: 4 times a day for 2 weeks 3 times a day for 2 weeks
	  ○ *Duration preoperative: days*: 0
	  ○ *Duration postoperative: days*: 28
	Type of surgery: Phacoemulsification

Outcomes	**Follow-up:** 1 month • CMO (OCT-verified but not defined) • Inflammation (Tyndall reaction, categorical)
Contact details	**Authors name:** Zhang HY **Institution:** Beijing Tongren Eye Center **Email:** NR **Address:** Beijing Tongren Eye Centre, Beijing Tongren Hospital, Capital Medical University; Beijing Ophthalmology and Visual Science Key Laboratory, Beijing 100730, China
Notes	**Funding source:** NR **Declaration of interest:** NR **Date study conducted:** NR **Trial registration number:** NR **Contacting study investigators:** Trial authors not contacted.

Zhang 2008 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Judgement comment: Not reported how list was generated. Trial described as "randomised" but with no further details
Allocation concealment (selection bias)	Unclear risk	Judgement comment: Not reported how allocation administered. Trial described as "randomised" but with no further details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: No information on masking. We assume that in absence of reporting on this patients and personnel were not masked
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: No information on masking. We assume that in absence of reporting on this outcome assessors were not masked
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: Missing data less than 20% (i.e. more than 80% follow-up) and equal follow-up in both groups and no obvious reason why loss to follow-up should be related to outcome
Selective reporting (reporting bias)	Unclear risk	Judgement comment: No access to protocol or trial registry entry

AE: adverse events
BCVA: best corrected visual acuity
CMO: cystoid macular oedema
CRT: corneal retinal thickness
DR: diabetic retinopathy
ECCE: extracapsular cataract extraction
IOL: intraocular lens
IOP: intraocular pressure
NR: not reported
NSAID: non-steroidal anti-inflammatory drug
OCT: optical coherence tomography
RCT: randomised controlled trial
SD: standard deviation

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

Study	Reason for exclusion
Abelson 1989	Not topical treatment.
Carenini 1993	Not RCT.
Chen 2015	Study only performed follow-up for 2 weeks in total.
Dehgan 1992	Not able to source paper.
Duong 2015	Not RCT.
Hendrikse 1982	Not able to source paper.
Hollwich 1983	Not relevant comparator.
ISRCTN02628492	Study was terminated due to lack of funding.
Miyake 2000	Probably not random allocation, unclear response from study author
Nishino 2009	Not relevant intervention.
Riley 2006	Not relevant intervention.
Sanders 1982	Not able to source paper.
Sellares 1992	Not able to source paper.
Sholiton 1979	Not topical treatment.
Tang 2015	Not relevant intervention.
Wolf 2007	Not RCT.
Yamaaki 1984	Not RCT.
Yilmaz 2012	Not RCT.

RCT: randomised controlled trial

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

CTRI/2009/091/001078

Methods	Parallel group RCT
Participants	Country: India 704 people aged 50 to 70 years within 40 kms of Vellore town Exclusion criteria: Inabiltity to visualise the macula preoperatively in the eye to be operated. Ocular disease that can affect macular function. Uncontrolled diabetics defined by RBS/PP Sugars > 200 mg/dl. Diabetic maculopathy with oedema in eye to be operated. Past history of intraocular surgery in the eye under consideration. History of use of topical steroid drops or NSAID drops within the past 30 days prior to enrolment. Current use of Oral steroids. Known NSAIDs allergy
Interventions	Intervention: ketorolac tromethamine Comparator: polyvinyl Alcohol
Outcomes	Primary outcome: • Acute pseudophakic cystoid macular oedema
Notes	September 2016: Study investigator confirms that this study is unpublished. We are awaiting a response to request for unpublished data

NSAID: non-steroidal anti-inflammatory drug

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

NCT01694212

Trial name or title	Preoperative topic diclofenac as a prevention of postoperative macular edema in patients with diabetic retinopathy
Methods	Parallel group RCT
Participants	Country: Croatia 120 people aged 60 to 90 years Inclusion criteria: • presence of nonproliferative diabetic retinopathy • presence of the cataract (LOCS 2-3) Exclusion criteria: • other chronic or acute eye diseases • hypersensitivity to any component of the diclofenac eye-drops patients on oral anticoagulant therapy • allergy to salycilates
Interventions	Intervention: diclofenac Comparator: placebo

NCT01694212 (*Continued*)

Outcomes	Primary Outcome: • change of central macular thickness at -7, 0, 1, 7, 30, 90 days after the cataract surgery measured with OCT Secondary Outcome: • progression of diabetic retinopathy -7 and 90 days after cataract surgery assessed on fundus photography (ETDRS) according to ETDRS criteria • IL-12 concentration immediately before cataract surgery measured in the sample of humour aqueous taken at the beginning of cataract surgery
Starting date	October 2012 End date: December 2016
Contact information	Ljubo Znaor, MD PhD, Clinical Hospital Center, Split
Notes	

NCT01774474

Trial name or title	PRevention of Macular EDema After Cataract Surgery (PREMED)
Methods	Parallel group RCT
Participants	Country: Netherlands 1135 people aged 21 years and older Inclusion criteria: • all patients undergoing routine phacoemulsification (one eye per patient) • willing and/or able to comply with the scheduled visits and other study procedures • able to communicate properly and understand instructions • accepting possible off-label use of intravitreal bevacizumab and/or subconjunctival preservative-free TA Exclusion criteria will be different for non-diabetic and diabetic patients. All ophthalmic exclusion criteria are applicable to the study eye only, unless stated otherwise General exclusion criteria for participation in this study are: 1. age below 21 years old; 2. participation in another clinical study; 3. post-traumatic cataract; 4. combined surgery; 5. functional monoculus; 6. previous ocular surgery; 7. progressive glaucoma with severe visual field defects, use of anti-glaucomatous medication or steroid-induced IOP elevation that required IOP-lowering treatment; 8. IOP $\geq$ 25 mmHg; 9. history of any intraocular inflammation or uveitis; 10. history of pseudoexfoliation syndrome, which is expected to cause preoperative complications; 11. history of Fuchs' endothelial dystrophy or cornea guttata 3+; 12. history of retinal vein occlusion; 13. any macular pathology that might influence visual acuity, other than diabetic macular oedema; 14. use of intravitreal bevacizumab or ranibizumab in the previous 6 weeks or intravitreal aflibercept in the previous 10 weeks;

NCT01774474 (*Continued*)

	15. use of intra- or periocular corticosteroid injection in the previous 4 months; 16. current use of topical NSAIDs or corticosteroids; 17. use of systemic corticosteroids (≥ 20 mg prednisolone or equivalence); 18. history of relevant adverse events, including serious adverse events, occurring after administration of NSAIDs, acetylsalicylic acid, sodium sulphite, corticosteroids or bevacizumab; 19. contraindications for use of topical NSAIDs, topical or subconjunctival corticosteroids or intravitreal bevacizumab or related drugs. Non-diabetic patients with a history of CME will be excluded from participation in the study. Additionally, diabetic patients will be excluded from participation in case of: 1. macular oedema with a CSMT ≥ 450 µm; 2. very severe non-proliferative diabetic retinopathy or proliferative diabetic retinopathy requiring panretinal photocoagulation or vitrectomy; 3. vitreous haemorrhage present during preoperative visit(s); 4. cerebrovascular accident, myocardial infarction or other thromboembolic events in the previous 3 months; 5. a history of recurrent thromboembolic events; 6. a history of severe systemic bleeding in the previous 3 months; 7. major surgery in the previous 3 months; 8. history of glaucoma.
Interventions	Intervention: bromfenac Intervention: bromfenac and dexamethasone Comparator: dexamethasone
Outcomes	Primary outcome: • change in central subfield mean macular thickness at 6 weeks postoperatively Secondary outcomes: • Clinically significant macular oedema at 12 weeks postoperatively Other outcome measures at 6 and 12 weeks see clinicaltrials.gov/ct2/show/NCT01774474
Starting date	July 2013 End date: October 2016
Contact information	Prof. Rudy MM Nuijts, MD, PhD rudy.nuijts@0mumc.nl Laura HP Wielders, MD laura.wielders@mumc.nl
Notes	

NCT02646072

Trial name or title	Effect of preoperative topical ketorolac on aqueous cytokine levels and macular thickness in cataract surgery patients
Methods	Parallel group RCT
Participants	Country: Malaysia 80 participants aged 18 to 90 years Inclusion criteria: Diabetic patient group

NCT02646072 (*Continued*)

	1. Type 2 diabetes mellitus with no diabetic retinopathy 2. If with comorbid, controlled hypertension with no hypertensive crisis in recent six months 3. Listed for phacoemulsification cataract surgery Non-diabetic patient group 1. No history of diabetes 2. If with comorbid, controlled hypertension with no hypertensive crisis in recent six months 3. Listed for phacoemulsification cataract surgery Exclusion criteria 1. Smoker 2. Presence of immune disease, local or systemic inflammation 3. Presence of retinal diseases, glaucoma 4. Previous surgical procedure on the eye 5. Intraoperative complications
Interventions	Intervention: ketorolac tromethamine Comparator: no intervention
Outcomes	Primary outcome: • Level of aqueous inflammatory cytokines post treatment as assessed using Bio-plex Pro Assays, 9 months Secondary outcome: • Changes from baseline in central subfield retinal thickness as assessed by OCT, 9 months
Starting date	August 2014 End date: June 2015
Contact information	Yin Peng Lai, Univerisity of Malaya
Notes	

CME: cystoid macular oedema (edema)
DR: diabetic retinopathy
ETDRS: early treatment diabetic retinopathy study
IOP: intraocular pressure
NSAID: non-steroidal anti-inflammatory drug
OCT: optical coherence tomography
RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. NSAIDs plus steroids versus steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Poor vision due to MO	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 3 months	5	1360	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.23, 0.76]
1.2 12 months	1	88	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.09, 20.37]
2 Central retinal thickness	9		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Change from baseline	3		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 FInal value	6		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Total macular volume	6	570	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.21, -0.07]
4 Macular oedema	21	3638	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.32, 0.49]
5 Inflammation	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 Inflammation (flare)	2	216	Mean Difference (IV, Fixed, 95% CI)	-1.41 [-2.30, -0.52]
7 BCVA	10		Mean Difference (IV, Random, 95% CI)	Totals not selected
7.1 Final value	7		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 Change from baseline	3		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. NSAIDs versus steroids

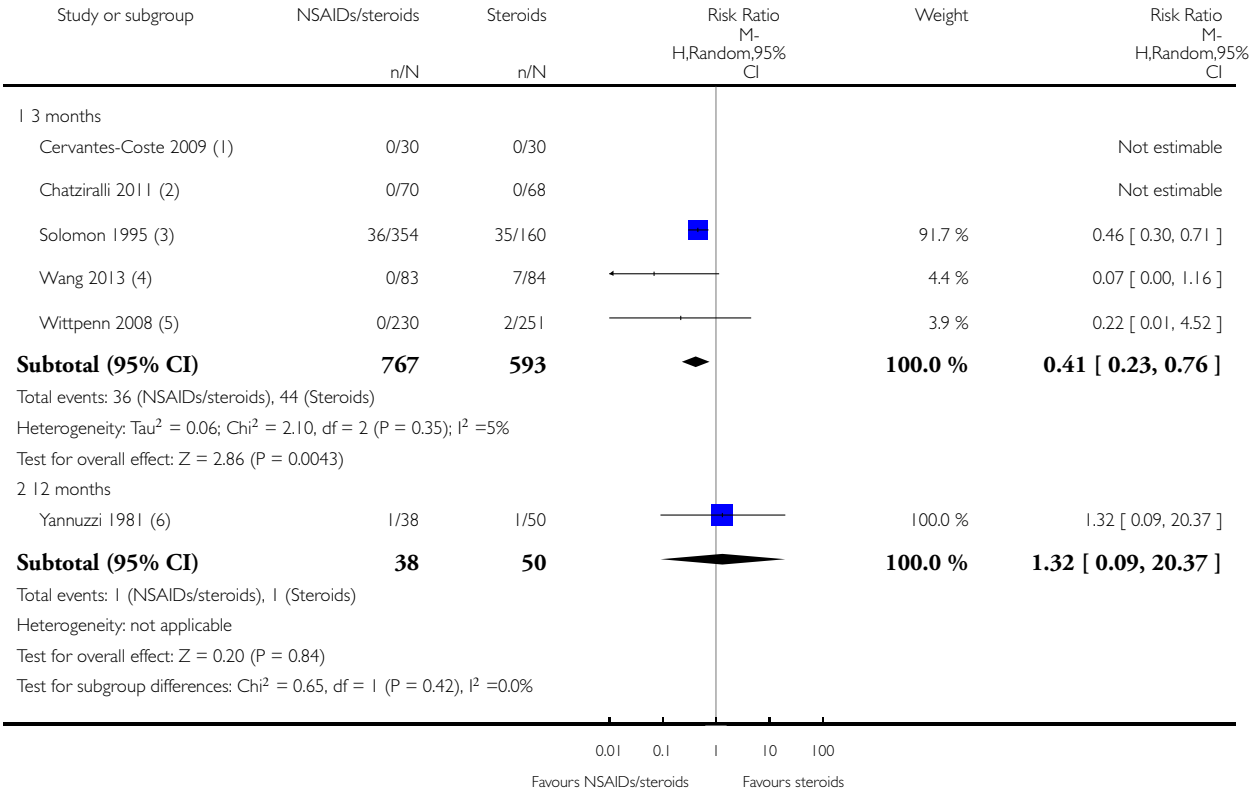
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Central retinal thickness	2	121	Mean Difference (IV, Fixed, 95% CI)	-22.64 [-38.86, -6.43]
2 Macular oedema	5	520	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.18, 0.41]
3 Inflammation (flare)	5		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 BCVA	3		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 NSAIDs plus steroids versus steroids, Outcome 1 Poor vision due to MO.

Review: Prophylactic non-steroidal anti-inflammatory drugs for the prevention of macular oedema after cataract surgery

Comparison: 1 NSAIDs plus steroids versus steroids

Outcome: 1 Poor vision due to MO



(1) Follow-up: 6 weeks, "clinically significant macular oedema associated with vision loss" (cutpoint not defined)

(2) Follow-up: 6 weeks, fundoscopy and Amsler grid test "no evidence of clinically significant CME"

(3) Follow-up: days 21-60, CMO on fluoresecein angiography with visual acuity <=20/40

(4) Follow-up: 2 months, OCT-confirmed CMO with "visual impairment" (not specified cutpoint)

(5) Follow-up: 4 weeks, OCT-confirmed CMO with visual acuity <6/9.

(6) Follow-up: 1 year, CMO on fluorescein angiography with visual acuity <6/60

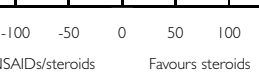
Analysis 1.2. Comparison 1 NSAIDs plus steroids versus steroids, Outcome 2 Central retinal thickness.

Review: Prophylactic non-steroidal anti-inflammatory drugs for the prevention of macular oedema after cataract surgery

Comparison: 1 NSAIDs plus steroids versus steroids

Outcome: 2 Central retinal thickness

Study or subgroup	NSAIDs/steroids N	Mean(SD)[microns]	Steroids N	Mean(SD)[microns]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Change from baseline						
Jung 2015 (1)	60	4.604 (5.2396)	31	12.47 (12.24)		-7.87 [-12.37, -3.36]
Mathys 2010 (2)	39	5.6 (13.8)	40	2.78 (12.9)		2.82 [-3.07, 8.71]
Singh 2012 (3)	125	18.9 (19.5)	126	40.8 (49)		-21.90 [-31.11, -12.69]
2 FInal value						
Cervantes-Coste 2009 (4)	30	194.43 (20.26)	30	203.86 (17.98)		-9.43 [-19.12, 0.26]
Li 2011 (5)	104	242.79 (20.75)	113	265.43 (29.3)		-22.64 [-29.35, -15.93]
Moschos 2012 (6)	38	152.3 (20.8)	41	152 (16.3)		0.30 [-7.98, 8.58]
Ticly 2014 (7)	37	282.08 (36.65)	44	279.05 (29.11)		3.03 [-11.58, 17.64]
Tzelikis 2015 (8)	45	282.26 (45.21)	40	274.82 (30.45)		7.44 [-8.79, 23.67]
Wang 2013 (9)	85	209.51 (29.014)	84	240.41 (49.274)		-30.90 [-43.11, -18.69]



(1) Follow-up: 1 month

(2) Follow-up: 2 months

(3) Follow-up: 90 days, "mean maximum change" from baseline

(4) Follow-up: 6 weeks

(5) Follow-up: 1 month

(6) Follow-up: 1 month

(7) Follow-up: 5 weeks

(8) Follow-up: 1 month

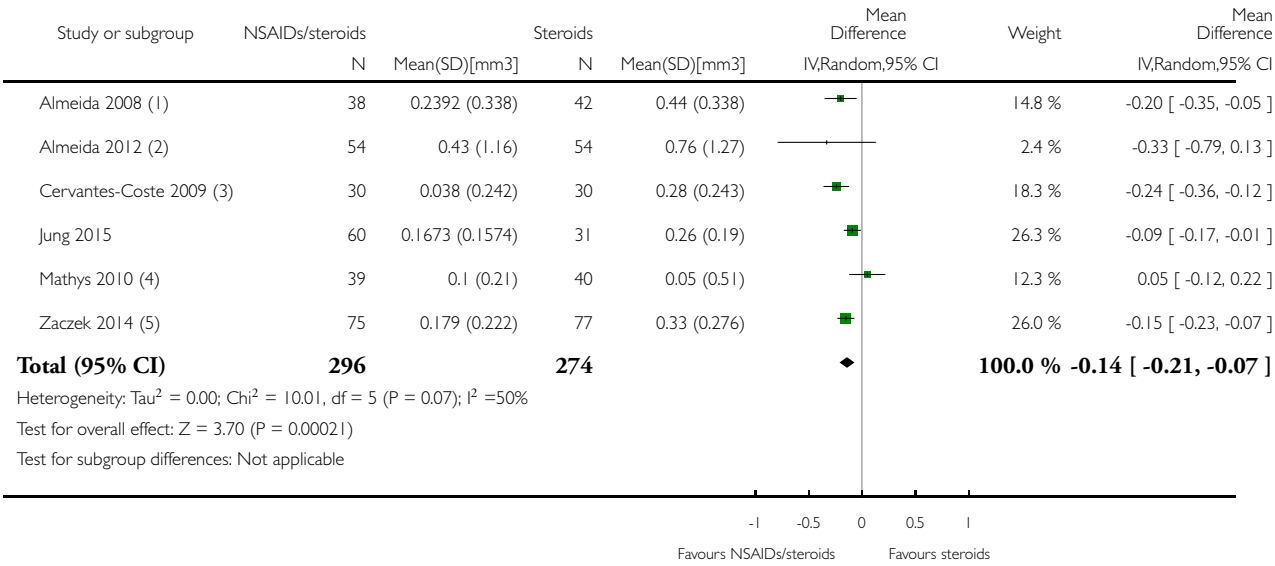
(9) Follow-up: 2 months

Analysis 1.3. Comparison 1 NSAIDs plus steroids versus steroids, Outcome 3 Total macular volume.

Review: Prophylactic non-steroidal anti-inflammatory drugs for the prevention of macular oedema after cataract surgery

Comparison: 1 NSAIDs plus steroids versus steroids

Outcome: 3 Total macular volume



(1) Follow-up: 1 month, change from baseline

(2) Follow-up: 1 month, change from baseline

(3) Follow-up: 6 weeks, change from baseline

(4) Follow-up: 2 months, change from baseline

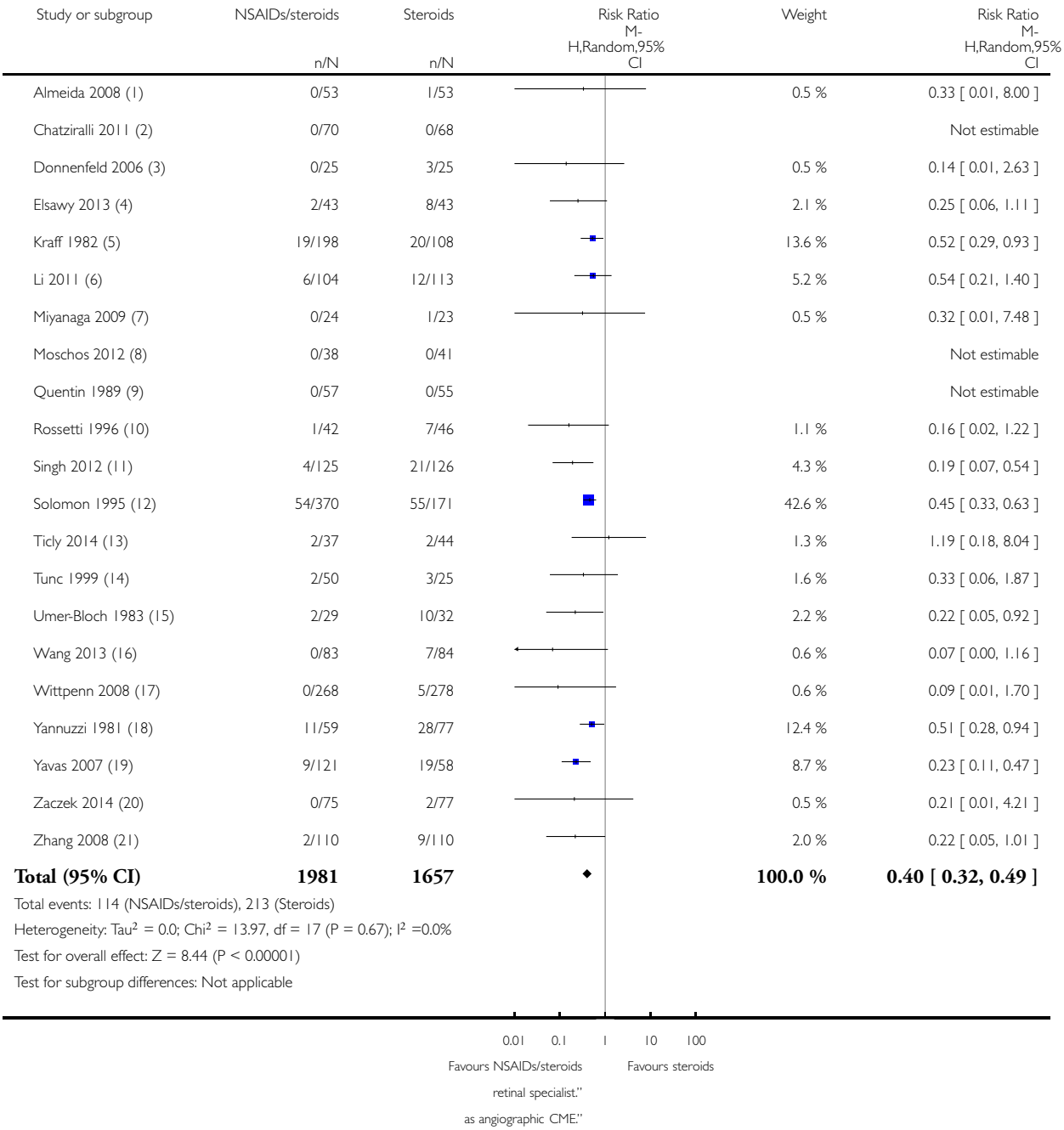
(5) Follow-up: 6 weeks, change from baseline

Analysis 1.4. Comparison 1 NSAIDs plus steroids versus steroids, Outcome 4 Macular oedema.

Review: Prophylactic non-steroidal anti-inflammatory drugs for the prevention of macular oedema after cataract surgery

Comparison: 1 NSAIDs plus steroids versus steroids

Outcome: 4 Macular oedema



retinal specialist."

as angiographic CME."

(1) Follow-up: 1 month. OCT used but CMO not defined.

(2) Follow-up: day 42. "Clinically significant MO" via fundoscopy and Amsler grid test.

(3) Follow-up: 2 weeks. "Clinically significant CME"

(4) Follow-up: 12 weeks. clinical examination, unclear if OCT-verified

(5) Follow-up: mean 4.1 (range 2.5 to 12 months), fluorescein angiography using Miyake 1977 classification

(6) Follow-up: 1 month. OCT , "clinically apparent" CME otherwise not defined

(7) Follow-up: 2 months, "obvious CMO confirmed by OCT"

(8) Follow-up: 1 month, "clinically significant CME" unclear if OCT-verified

(9) Follow-up: 180 days, fluorescein angiography using Miyake 1977 classification

(10) Follow-up: 6 months, fluorescein angiography using Miyake 1977 classification

(11) Follow-up: 90 days, >=30% increase in central subfield macular thickness from baseline

(12) Follow-up: days 21-60: "angiographic CME"

(13) Follow-up: 5 weeks, fluorescein angiography using Miyake 1977 classification

(14) Follow-up: 2 months. "clinically significant" FFA plus drop in 1 line Snellen acuity since 2 weeks postop

(15) Follow-up: 12 weeks, fluorescein angiography using Miyake 1977 classification

(16) Follow-up: 2 months, "CME was defined as central retinal thickness >250 μ m and the presence of intraretinal cystoid spacebeneath the foveal, with the diagnosis confirmed by the same

(17) Follow-up: 4 weeks. clinical and OCT-based

(18) Follow-up: 10 weeks, fluorescein angiography, CMO not defined

(19) Follow-up: 3 months, "Slight fluorescein leakage into the cystic space without enclosing the entire centralfovea or complete fluorescein accumulation in the cysticspace was diagnosed

(20) Follow-up: 6 weeks, OCT verified but not defined

(21) Follow-up: 1 month, OCT verified but not defined

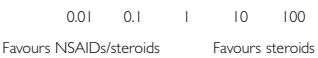
Analysis 1.5. Comparison 1 NSAIDs plus steroids versus steroids, Outcome 5 Inflammation.

Review: Prophylactic non-steroidal anti-inflammatory drugs for the prevention of macular oedema after cataract surgery

Comparison: 1 NSAIDs plus steroids versus steroids

Outcome: 5 Inflammation

Study or subgroup	NSAIDs/steroids n/N	Steroids n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Cervantes-Coste 2009 (1)	0/30	0/30		Not estimable
Chatziralli 2011 (2)	2/70	0/68		4.86 [0.24, 99.39]
Zhang 2008 (3)	0/110	21/110		0.02 [0.00, 0.38]



(1) Follow-up: 6 weeks, "inflammatory cells greater than 1+ during first week of postoperative visits.

(2) Follow-up: day 28, corneal oedema or Tyndall reaction or conjunctival hyperemia, by day 35 had disappeared.

(3) Follow-up: 1 month, Tyn granule +

Analysis 1.6. Comparison 1 NSAIDs plus steroids versus steroids, Outcome 6 Inflammation (flare).

Review: Prophylactic non-steroidal anti-inflammatory drugs for the prevention of macular oedema after cataract surgery

Comparison: 1 NSAIDs plus steroids versus steroids

Outcome: 6 Inflammation (flare)

Study or subgroup	NSAIDs/steroids N	Mean(SD)[photons/ms]	Steroids N	Mean(SD)[photons/ms]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Miyanaga 2009 (1)	24	5.2 (2.2)	23	8.5 (6.5)		10.1 %	-3.30 [-6.10, -0.50]
Wang 2013 (2)	85	6.6226 (2.5515)	84	7.82 (3.5854)		89.9 %	-1.20 [-2.14, -0.26]
Total (95% CI)	**109**		**107**			**100.0 %**	**-1.41 [-2.30, -0.52]**

Heterogeneity: Chi^2 = 1.95, df = 1 (P = 0.16); I^2 =49%

Test for overall effect: Z = 3.10 (P = 0.0019)

Test for subgroup differences: Not applicable

(1) Follow-up: 2 months

(2) Follow-up: 2 months

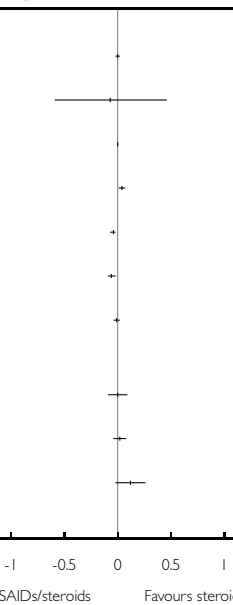
Analysis 1.7. Comparison 1 NSAIDs plus steroids versus steroids, Outcome 7 BCVA.

Review: Prophylactic non-steroidal anti-inflammatory drugs for the prevention of macular oedema after cataract surgery

Comparison: 1 NSAIDs plus steroids versus steroids

Outcome: 7 BCVA

Study or subgroup	NSAIDs/steroids N	Mean(SD)[logMAR]	Steroids N	Mean(SD)[logMAR]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Final value						
Chatziralli 2011 (1)	70	0.03 (0.05)	68	0.03 (0.06)		0.0 [-0.02, 0.02]
Miyanaga 2009 (2)	24	0.01 (1.3)	23	0.08 (0.08)		-0.07 [-0.59, 0.46]
Moschos 2012 (3)	38	0 (0.01)	41	0 (0.01)		0.0 [0.00, 0.00]
Tzelikis 2015 (4)	86	0.0505 (0.1107)	40	0.01 (0.05)		0.04 [0.01, 0.07]
Wang 2013 (5)	85	0.045 (0.061)	84	0.09 (0.1059)		-0.04 [-0.07, -0.02]
Yavas 2007 (6)	121	0.0547 (0.1209)	58	0.11 (0.12)		-0.06 [-0.09, -0.02]
Zaczek 2014 (7)	75	-0.06 (0.091)	77	-0.05 (0.091)		-0.01 [-0.04, 0.02]
2 Change from baseline						
Almeida 2012 (8)	54	-0.22 (0.23)	54	-0.22 (0.23)		0.0 [-0.09, 0.09]
Mathys 2010 (9)	39	-0.3 (0.13)	40	-0.32 (0.13)		0.02 [-0.04, 0.08]
Ticly 2014 (10)	37	-0.52 (0.32)	44	-0.64 (0.3)		0.12 [-0.02, 0.26]



(1) Follow-up: 6 weeks, final value

(2) Follow-up: 2 months, final value

(3) Follow-up: 1 month, final value

(4) Follow-up: 30 days, final value

(5) Follow-up: 2 months, final value

(6) Follow-up: 3 months, final value

(7) Follow-up: 6 weeks. final value, SD estimated from p-value

(8) Follow-up: 1 month

(9) Follow-up: 2 months, SD estimated from p-value

(10) Follow-up: 5 weeks

Analysis 2.1. Comparison 2 NSAIDs versus steroids, Outcome 1 Central retinal thickness.

Review: Prophylactic non-steroidal anti-inflammatory drugs for the prevention of macular oedema after cataract surgery

Comparison: 2 NSAIDs versus steroids

Outcome: 1 Central retinal thickness

Study or subgroup	NSAIDs N	Mean(SD)[microns]	Steroids N	Mean(SD)[microns]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Endo 2010 (1)	31	216.9 (19.8)	31	236.1 (63.6)		47.8 %	-19.20 [-42.65, 4.25]
Miyake 2011 (2)	30	194.3 (20.7)	29	220.1 (58.2)		52.2 %	-25.80 [-48.24, -3.36]
Total (95% CI)	**61**		**60**			**100.0 %**	**-22.64 [-38.86, -6.43]**

Heterogeneity: $Chi^2 = 0.16$, df = 1 (P = 0.69); $I^2 = 0.0\%$

Test for overall effect: Z = 2.74 (P = 0.0062)

Test for subgroup differences: Not applicable

(1) Follow-up: 6 weeks, final value

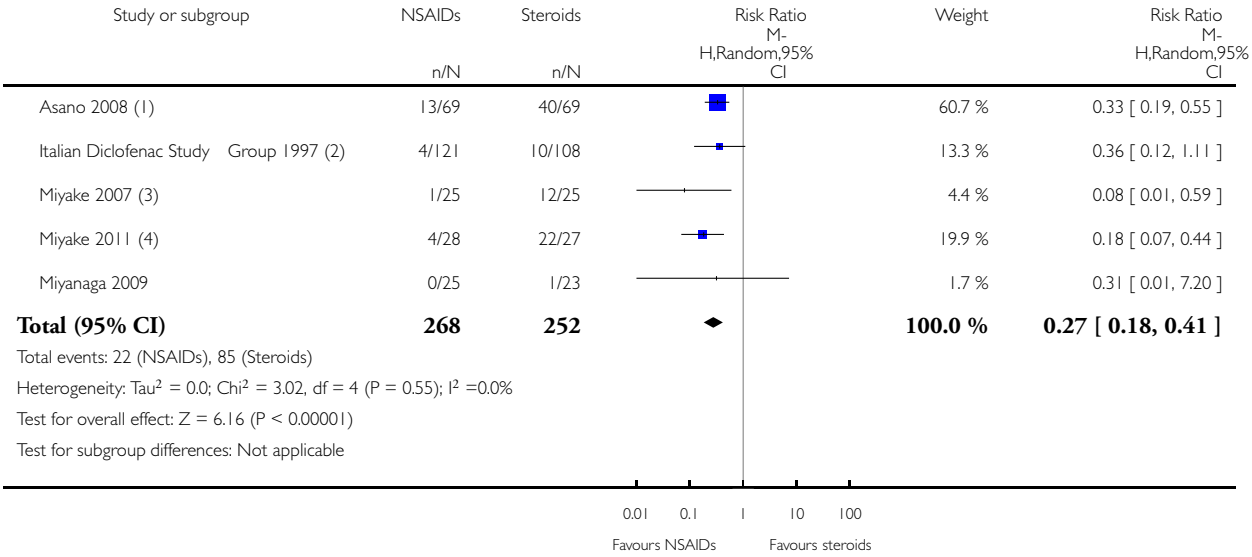
(2) Follow-up: 5 weeks

Analysis 2.2. Comparison 2 NSAIDs versus steroids, Outcome 2 Macular oedema.

Review: Prophylactic non-steroidal anti-inflammatory drugs for the prevention of macular oedema after cataract surgery

Comparison: 2 NSAIDs versus steroids

Outcome: 2 Macular oedema



(1) Follow-up: 5 weeks, fluorescein angiography using Miyake 1977 classification

(2) Follow-up: 140 days, fluorescein angiography using Miyake 1977 classification

(3) Follow-up: 5 weeks, fluorescein angiography using Miyake 1977 classification

(4) Follow-up: 5 weeks, fluorescein angiography using Miyake 1977 classification

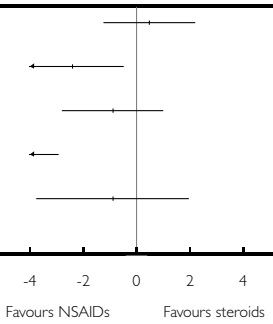
Analysis 2.3. Comparison 2 NSAIDs versus steroids, Outcome 3 Inflammation (flare).

Review: Prophylactic non-steroidal anti-inflammatory drugs for the prevention of macular oedema after cataract surgery

Comparison: 2 NSAIDs versus steroids

Outcome: 3 Inflammation (flare)

Study or subgroup	NSAIDs		Steroids		Mean Difference	Mean Difference
	N	Mean(SD)[photon/ms]	N	Mean(SD)[photon/ms]	IV,Random,95% CI	IV,Random,95% CI
Asano 2008 (1)	65	8.45 (5.99)	62	7.98 (3.78)		0.47 [-1.26, 2.20]
Endo 2010 (2)	31	3.9 (3.75)	31	6.3 (4)		-2.40 [-4.33, -0.47]
Miyake 2007 (3)	25	8.1 (3.8)	25	9 (3)		-0.90 [-2.80, 1.00]
Miyake 2011 (4)	30	12 (5.5)	29	19.3 (10.7)		-7.30 [-11.66, -2.94]
Miyanaga 2009	25	7.6 (2.8)	23	8.5 (6.5)		-0.90 [-3.77, 1.97]



(1) Follow-up: 8 weeks

(2) Follow-up: 5 weeks

(3) Follow-up: 8 weeks

(4) Follow-up: 5 weeks

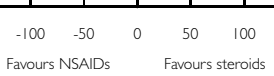
Analysis 2.4. Comparison 2 NSAIDs versus steroids, Outcome 4 BCVA.

Review: Prophylactic non-steroidal anti-inflammatory drugs for the prevention of macular oedema after cataract surgery

Comparison: 2 NSAIDs versus steroids

Outcome: 4 BCVA

Study or subgroup	NSAIDs		Steroids		Mean Difference	Mean Difference
	N	Mean(SD)[logMAR]	N	Mean(SD)[logMAR]	IV,Random,95% CI	IV,Random,95% CI
Asano 2008 (1)	58	-0.071 (0.08)	52	-0.07 (0.078)		0.00 [-0.03, 0.02]
Endo 2010 (2)	31	-0.09 (0.056)	31	-0.04 (0.085)		-0.05 [-0.09, -0.01]
Miyanaga 2009 (3)	25	0.115 (0.03)	23	0.08 (0.08)		0.04 [0.01, 0.07]



(1) Follow-up: 8 weeks, final value

(2) Follow-up: 6 weeks

(3) Follow-up: 2 months

ADDITIONAL TABLES

Table 1. 'Risk of bias' assessment

Domain	Risk of bias		
	Low	Unclear	High
Sequence generation	Computer-generated list, random table, other method of generating random list	Not reported how list was generated. Trial may be described as "randomised" but with no further details	Alternate allocation, date of birth, records (these RCTs should be excluded)
Allocation concealment	Central centre (web/telephone access), sealed opaque envelopes	Not reported how allocation administered. Trial may be described as "randomised" but with no further details	Investigator involved in treatment allocation or treatment allocation clearly not masked
Blinding of participants and personnel	Clearly stated that participants and personnel not aware of which treatment received	Described as "double-blind" with no information on who was masked	Open-label or no information on masking. We assume that in absence of reporting on this outcome, patients and personnel were not masked

Table 1. 'Risk of bias' assessment (*Continued*)

Blinding of outcome assessors	Clearly stated that outcome assessors were masked.	Described as "double-blind" with no information on who was masked	Open-label or no information on masking. We assume that in absence of reporting on this outcome, assessors were not masked
Incomplete outcome data	Missing data less than 20% (i.e. more than 80% follow-up) and equal follow-up in both groups and no obvious reason why loss to follow-up should be related to outcome	Follow-up not reported or missing data > 20% (i.e. follow-up < 80%) but follow-up equal in both groups	Follow-up different in each group and/or related to outcome.
Selective outcome reporting	All outcomes in protocol and/or trial registry entry are reported	No access to protocol or trial registry entry.	Outcomes in protocol and/or trial registry entry selectively reported
Other sources of bias Note: we did not identify any important sources of other bias so this domain is omitted from the risk of bias tables	No other source of bias.	Trial stopped early due to poor recruitment. Baseline imbalance, but not clear that it is important.	Trial stopped early because of outcome. Important baseline imbalance that might have an effect on the results

Table 2. Studies

	Study	Country	Open-label	Funding sources	Declaration of interest	Trial registration	Abstract only
1	Almeida 2008	Canada	Yes	Non-industry	Reported; no CoI	NCT00335439	No
2	Almeida 2012	Canada	No	Non-industry	Reported; no CoI	NCT01395069	No
3	Asano 2008	Japan	No	Not reported	Reported; no CoI	Not registered	No
4	Brown 1996	USA	No	Industry	Not reported	Not registered	No
5	Cervantes-Coste 2009	Mexico	No	Not reported	Reported; no CoI	Not registered	No
6	Chatziralli 2011	Greece	No	Not reported	Not reported	Not registered	No
7	Donnenfeld 2006	USA	No	Industry/Non-Industry	CoI	Not registered	No

Table 2. Studies (*Continued*)

8	Elsawy 2013	Egypt	No	Not reported	Reported; no CoI	Not registered	No
9	Endo 2010	Japan	Yes	Not reported	Reported; no CoI	Not registered	No
10	Italian Diclofenac Study Group 1997	Italy	No	Not reported	CoI	Not registered	No
11	Jung 2015	South Korea	No	Non-industry	Reported; no CoI	Not registered	No
12	Kraff 1982	USA	No	Non-industry	Not reported	Not registered	No
13	Li 2011	China	No	Not reported	Not reported	Not registered	No
14	Mathys 2010	USA	No	Non-industry	Reported; no CoI	NCT00494494	No
15	Miyake 2007	Japan	No	Not reported	Reported; no CoI	Not registered	No
16	Miyake 2011	Japan	No	Not reported	CoI	Not registered	No
17	Miyanaga 2009	Japan	No	Not reported	Not reported	Not registered	No
18	Moschos 2012	Greece	No	Not reported	Reported; no CoI	Not registered	No
19	Quentin 1989	Germany	No	Not reported	Not reported	Not registered	No
20	Rossetti 1996	Italy	No	Not reported	Reported; no CoI	Not registered	No
21	Singh 2012	USA	No	Not reported	CoI	NCT00782717	No
22	Solomon 1995	Canada (8 sites) and Germany (2 sites)	No	Industry	Reported; no CoI	Not registered	No
23	Tauber 2006	USA	No	Industry	CoI	Not registered	Yes
24	Ticly 2014	Brazil	No	Not reported	Reported; no CoI	Not registered	No
25	Tunc 1999	Turkey	No	Not reported	Not reported	Not registered	No

Table 2. Studies (*Continued*)

26	Tzelikis 2015	Brazil	No	Not reported	Reported; no CoI	NCT02084576	No
27	Umer-Bloch 1983	Switzerland	No	Not reported	Not reported	Not registered	No
28	Wang 2013	China	Yes	Non-industry	Not reported	Not registered	No
29	Wittpenn 2008	USA	No	Industry	CoI	NCT00348244	No
30	Yannuzzi 1981	USA	No	Non-industry	Not reported	Not registered	No
31	Yavas 2007	Turkey	No	Not reported	Reported; no CoI	Not registered	No
32	Yung 2007	USA	No	Not reported	Not reported	Not registered	No
33	Zaczek 2014	Sweden	No	Industry/Non-industry	Reported; no CoI	Not registered	No
34	Zhang 2008	China	No	Not reported	Not reported	Not registered	No

CoI: conflict of interest

Table 3. Participant numbers

	Study	Number of people randomised	Number of people randomised (missing data imputed)*	Number of eyes	Number of eyes estimated (missing data imputed)*	Number of people followed up	Number of people followed up (missing data imputed)*	Percentage follow-up	Eyes per person enrolled in the trial
1	Almeida 2008	98	98	106	106	-	74	75%	106 eyes of 98 people
2	Almeida 2012	193	193	-	193	162	162	84%	Probably one
3	Asano 2008	150	150	150	150	142	142	95%	One eye
4	Brown 1996	-	-	-	-	-		-	Probably one
5	Cervantes-Coste 2009	60	60	60	60	60	60	100%	One eye

Table 3. Participant numbers (*Continued*)

6	Chatziralli 2011	145	145	145	145	138	138	95%	Probably one
7	Donnenfeld 2006	100	100	-	100	-	100	-	Unclear
8	Elsawy 2013	70	70	86	86	-	86	-	86 eyes of 70 patients
9	Endo 2010	75	75	75	75	62	62	83%	One eye
10	Italian Diclofenac Study Group 1997	281	281	281	281	229	229	81%	One eye
11	Jung 2015	91	91	91	91	Not reported	91	Not reported	One eye
12	Kraff 1982	500	500	-	500	492	492	98%	Unclear
13	Li 2011	217	217	217	217	-	217	-	One eye
14	Mathys 2010	84	84	84	84	79	79	94%	One eye
15	Miyake 2007	62	62	62	62	50	50	81%	Probably one
16	Miyake 2011	60	60	60	60	55	55	92%	One eye
17	Miyanaga 2009	72	72	72	72	-	72	-	One eye
18	Moschos 2012	79	79	79	79	-	79	-	One eye
19	Quentin 1989	179	179	179	179	112	112	63%	One eye
20	Rossetti 1996	88	88	88	88	-	88	-	Probably one
21	Singh 2012	263	263	263	263	251	251	95%	One eye

Table 3. Participant numbers (*Continued*)

22	Solomon 1995	681	681	681	681	364	364	53%	Probably one
23	Tauber 2006	-	32	-	32	32	32	-	Unclear
24	Ticly 2014	91	91	91	91	81	81	89%	Probably one
25	Tunc 1999	75	75	75	75	75	75	-	One eye
26	Tzelikis 2015	142	142	142	142	126	126	89%	One eye
27	Umer-Bloch 1983	-	73	-	73	73	73	-	Unclear
28	Wang 2013	240	240	-	240	167	167	70%	Unclear
29	Wittpenn 2008	546	546	546	546	478	478	88%	One eye
30	Yannuzzi 1981	-	201	231	231	-	231	59%	231 eyes of 210 people
31	Yavas 2007	189	189	189	189	179	179	95%	One eye; right eye only
32	Yung 2007	37	37	-	37	-	37	-	Unclear
33	Zaczek 2014	160	160	160	160	152	152	95%	One eye
34	Zhang 2008	-	198	220	220	-	220	100%	220 eyes of 198 people

*For studies that did not report the number randomised, we have estimated this from the number followed up. For studies that did not report the number followed up, we have estimated this from the numbers randomised. Number of eyes estimated assuming one eye per person, if not clearly stated otherwise.

Table 4. Participant characteristics

	Study	Average age	Age range	% female	% with diabetes	% with uveitis
1	Almeida 2008	72	45 to 92	61%	21%	1%
2	Almeida 2012	72	50 to 88	54%	- but low risk population	"low risk population"
3	Asano 2008	66	-	56%	0% people with diabetes excluded	0% people with uveitis excluded
4	Brown 1996	-	-	-	- but people with DR excluded	0% people with uveitis excluded
5	Cervantes-Coste 2009	72	51 to 88	64%	20%	0% people with uveitis excluded
6	Chatziralli 2011	74	-	40%	10%	0% people with uveitis excluded
7	Donnenfeld 2006	73	-	55%	0% people with diabetes excluded	0% people with uveitis excluded
8	Elsawy 2013	-	-	37%	100%	-
9	Endo 2010	69	37 to 84	45%	100%	0% people with uveitis excluded
10	Italian Diclofenac Study Group 1997	68	-	52%	-	-
11	Jung 2015	67	-	55%	26%	-
12	Kraff 1982	69	37 to 97	57%	-	-
13	Li 2011	72	-	63%	100%	-
14	Mathys 2010	72	44 to 90	54%	0% people with diabetes excluded	0% people with uveitis excluded
15	Miyake 2007	66	-	54%	0% people with diabetes excluded	0% people with uveitis excluded
16	Miyake 2011	65	48 to 82	46%	9%	0% people with uveitis excluded
17	Miyanaga 2009	72	41 to 86	71%	0% people with diabetes excluded	0% people with uveitis excluded
18	Moschos 2012	77	-	66%	0% people with diabetes excluded	0% people with uveitis excluded

Table 4. Participant characteristics (*Continued*)

19	Quentin 1989	73	-	55%	- but people with DR excluded	0% people with uveitis excluded
20	Rossetti 1996	74	-	64%	0% people with diabetes excluded	-
21	Singh 2012	67	32 to 87	63%	100%	0% people with uveitis excluded
22	Solomon 1995	68	39 to 100	53%	-	0% people with uveitis excluded
23	Tauber 2006	-	-	-	-	-
24	Ticly 2014	67	-	47%	0% people with diabetes excluded	0% people with uveitis excluded
25	Tunc 1999	61	-	39%	0% people with diabetes excluded	0% people with uveitis excluded
26	Tzelikis 2015	-	-	-	-	-
27	Umer-Bloch 1983	69	-	52%	- but people with DR excluded	0% people with uveitis excluded
28	Wang 2013	73	46 to 92	54%	0% people with diabetes excluded	0% people with uveitis excluded
29	Wittpenn 2008	70	-	53%	-	-
30	Yannuzzi 1981	-	-	-	-	-
31	Yavas 2007	65	-	40%	0% people with diabetes excluded	0% people with uveitis excluded
32	Yung 2007	-	-	-	100%	-
33	Zaczek 2014	69	-	65%	-	-
34	Zhang 2008	-	-	-	-	-

DR: diabetic retinopathy

Table 5. Interventions

	Study	Type of cataract surgery	Comparison	NSAIDs	Steroid	Placebo in comparator group	Type of placebo
1	Almeida 2008	Phacoemulsification	NSAIDs plus steroids versus steroids	Ketorolac 0.5%	Prednisolone 1%	No	-
2	Almeida 2012	Phacoemulsification	NSAIDs plus steroids versus steroids	Ketorolac 0.5%, Nepafenac 0.1%	Prednisolone 1%	Yes	Sterile saline drops
3	Asano 2008	Phacoemulsification	NSAIDs versus steroids	Diclofenac 0.1%	Betamethasone 0.1%	No	-
4	Brown 1996	Phacoemulsification	NSAIDs versus steroids	Diclofenac 0.1%	Prednisolone 1%	No	-
5	Cervantes-Coste 2009	Phacoemulsification	NSAIDs plus steroids versus steroids	Nepafenac 0.1%	Dexamethasone (combined with tobramycin)	No	-
6	Chatziralli 2011	Phacoemulsification	NSAIDs plus steroids versus steroids	Ketorolac 0.5%	Dexamethasone 0.1% (combined with tobramycin 0.3%)	No	-
7	Donnenfeld 2006	Phacoemulsification	NSAIDs plus steroids versus steroids	Ketorolac 0.4%	Prednisolone 1%	Yes	Vehicle
8	Elsawy 2013	Phacoemulsification	NSAIDs plus steroids versus steroids	Ketorolac 0.4%	Dexamethasone 0.1%,	No	-
9	Endo 2010	Phacoemulsification	NSAIDs versus steroids	Bromfenac	Betamethasone (with fradiomycin sulfate) followed by fluorometholone	No	-
10	Italian Diclofenac Study Group 1997	ECCE	NSAIDs versus steroids	Diclofenac 0.1%	Dexamethasone 0.1%	Yes	Not specified

Table 5. Interventions (*Continued*)

11	Jung 2015	Phacoemulsification	NSAIDs versus steroids	Bromfenac 0.1%, Ketorolac 0.4%	Prednisolone acetate 1%	No	-
12	Kraff 1982	ECCE and phacoemulsification	NSAIDs plus steroids versus steroids	Indomethacin	Dexamethasone (in combination with neomycin sulfate, polymyxin B sulfate) for 4 days followed by dexamethasone alone for 4 weeks followed by fluorometholone for at least 6 months	Yes	Vehicle
13	Li 2011	Phacoemulsification	NSAIDs plus steroids versus steroids	Diclofenac 1%	Dexamethasone (combined with tobramycin)	No	-
14	Mathys 2010	Phacoemulsification	NSAIDs plus steroids versus steroids	Nepafenac 0.1%	Prednisolone 1%	No	-
15	Miyake 2007	Phacoemulsification	NSAIDs versus steroids	Diclofenac 0.1%	Fluorometholone 0.1%	No	-
16	Miyake 2011	Phacoemulsification	NSAIDs versus steroids	Nepafenac 0.1%	Fluorometholone 0.1%	No	-
17	Miyanaga 2009	Phacoemulsification	NSAIDs plus steroids versus steroids/ NSAIDs versus steroids	Bromfenac 0.1%	Betamethasone 0.1%, fluorometholone	No	-
18	Moschos 2012	Phacoemulsification	NSAIDs plus steroids versus steroids	Diclofenac 0.1%	Dexamethasone 0.1% (combined with chloramphenicol 0.5%)	No	-
19	Quentin 1989	ICCE	NSAIDs plus steroids versus	Diclofenac 0.1%	Dexamethasone	Yes	Not specified

Table 5. Interventions (*Continued*)

			steroids				
20	Rossetti 1996	ECCE	NSAIDs plus steroids versus steroids	Diclofenac	Dexamethasone (combined with tobramycin)	Yes	Not specified
21	Singh 2012	Phacoemulsification	NSAIDs plus steroids versus steroids	Nepafenac 1%	Prednisolone	Yes	Vehicle
22	Solomon 1995	ECCE	NSAIDs plus steroids versus steroids	Flurbiprofen 0.03% Indomethacin 1%	Prednisolone	Yes	Vehicle
23	Tauber 2006	Phacoemulsification	NSAIDs plus steroids versus steroids	Ketorolac 0.4%	Prednisolone 1%	No	-
24	Ticly 2014	Phacoemulsification	NSAIDs plus steroids versus steroids	Ketorolac 0.4%	Prednisolone 1%	Yes	Dextran 70/ hypromellose
25	Tunc 1999	ECCE	NSAIDs plus steroids versus steroids	Diclofenac 0.1%	Dexamethasone 1%	No	-
26	Tzelikis 2015	Phacoemulsification	NSAIDs plus steroids versus steroids	Ketorolac 0.4%, Nepafenac 0.1%	Prednisolone 1%	Yes	Artificial tears
27	Umer-Bloch 1983	ECCE/ICCE	NSAIDs plus steroids versus steroids	Indomethacin 1%	Dexamethasone (combined with either chloramphenicol or neomycin)	Yes	Vehicle
28	Wang 2013	Phacoemulsification	NSAIDs plus steroids versus steroids	Bromfenac 0.1%	fluorometholone 0.1% and dexamethasone 0.1%	No	-
29	Wittpenn 2008	Phacoemulsification	NSAIDs plus steroids versus steroids	Ketorolac 0.4%	Prednisolone 1%	Yes	Artificial tears
30	Yannuzzi 1981	ICCE	NSAIDs plus steroids versus steroids	Indomethacin 1%	Steroids given as part of standard care, not specified exactly	Yes	Vehicle

Table 5. Interventions (*Continued*)

					what		
31	Yavas 2007	Phacoemulsification	NSAIDs plus steroids versus steroids	Indomethacin 0.1%	Prednisolone 1%	No	-
32	Yung 2007	Phacoemulsification	NSAIDs plus steroids versus steroids	Ketorolac 0.5%	Prednisolone 1%	Yes	Artificial tears
33	Zaczek 2014	Phacoemulsification	NSAIDs plus steroids versus steroids	Nepafenac 0.1%	Dexamethasone 0.1%	Yes	Artifical tears
34	Zhang 2008	Phacoemulsification	NSAIDs plus steroids versus steroids	Pranoprofen	Dexamethasone (combined with tobramycin)	No	-

ECCE: extracapsular cataract extraction
ICCE: intracapsular cataract extraction
NSAIDs: non-steroidal anti-inflammatory drugs

Table 6. Outcomes

		Poor vision outcome due to MO	Quality of life/patient satisfaction	Central retinal thickness	Adverse effects reported	CMO	Inflammation	BCVA	Additional outcomes
Study	**Follow-up**	Analysis 1.1	No analysis; only one study reported this	Analysis 1.2; Analysis 2.1	Table 7	Analysis 1.4; Analysis 2.2	Analysis 1.5; Analysis 1.6; Analysis 2.3	Analysis 1.7; Analysis 2.4	Analysis 1.3
Almeida 2008	1 month				Yes	OCT used but CMO not defined			Change in total macular volume
Almeida 2012	1 month		COMTOL questionnaire	Mean change reported but not possible to calculate SD				LogMAR	Change in total macular volume; change in average macular

Table 6. Outcomes (*Continued*)

									cube thickness
Asano 2008	8 weeks				Yes	Fluorescein angiography using Miyake 1977 classification (at 5 weeks only)	Laser flare-cell photometry, mean value of anterior chamber flare (photons/millisecond)	LogMAR, final value	
Brown 1996	1 month						Laser flare-cell photometry, mean value of anterior chamber flare reported (photons) but was not possible to calculate SD		
Cervantes-Coste 2009	6 weeks	Quote: "None of the patients developed clinically significant macular oedema associated with vision loss"		Final value	Yes	Only reported CMO associated with vision loss	"Inflammatory cells greater than 1+ during first week of postoperative visits"		Total macular volume
Chatziralli 2011	6 weeks	Fundoscopy and Amsler grid test Quote: "no evidence of			Yes	"No evidence of clinically significant CME was detected in any patient via fun-	Corneal oedema or Tyndall reaction or conjunctival hyperaemia	LogMAR, final value	

Table 6. Outcomes (*Continued*)

		clinically significant CME“				doscopy and the Amsler grid test“			
Donnenfeld 2006	3 months				Yes	”Clinically significant CME“ but otherwise not defined, at 2 weeks only	”Mean inflammation score“ but was not possible to calculate SD	LogMAR, final value but could not extract data on SD	
Elsawy 2013	12 weeks					Clinical examination, unclear if OCT-verified			
Endo 2010	6 weeks			Final value	Yes		Anterior chamber flare values, photon count per millisecond	LogMAR, final value	
Italian Diclofenac Study Group 1997	140 days				Yes	Fluorescein angiography using Miyake 1977 classification			
Jung 2015	1 month			Change	Yes		”Inflammatory score“ (sum of anterior chamber cells and flare grade”		Change in macular volume
Kraff 1982	Between 2.5 and 12 months				Yes	Fluorescein angiography us-		Snellen acuity only, not included	

Table 6. Outcomes (*Continued*)

						ing Miyake 1977 classification		in analyses	
Li 2011	1 month			Final value		OCT, "clinically apparent" CME otherwise not defined		Snellen acuity only, not included in analyses	
Mathys 2010	2 months			Change from baseline	Yes			LogMAR	Change in foveal thickness, change in macular volume
Miyake 2007	5 weeks					Fluorescein angiography using Miyake 1977 classification	Unit of measurement unclear	Snellen acuity only, not included in analyses	
Miyake 2011	5 weeks			Final value	Yes	Fluorescein angiography using Miyake 1977 classification	Flare (photons/millisec), final value		Change in logMAR BCVA, categorical 3+, 2, 1 lines increase and no change
Miyanaga 2009	2 months				Yes	"Obvious CMO confirmed by OCT"	Aqueous flare (photons/millisecond)	LogMAR, final value	
Moschos 2012	1 month			Final value				LogMAR, final value	
Quentin 1989	180 days				Yes	Fluorescein angiography using Miyake 1977 classification		Snellen acuity only, not included in analyses	

Table 6. Outcomes (*Continued*)

Rossetti 1996	6 months				Yes	Fluorescein angiography using Miyake 1977 classification		Snellen acuity only, not included in analyses	
Singh 2012	90 days			Change from baseline	Yes	">= 30% increase in central subfield macular thickness from baseline"	Flare mentioned but data not reported	Corrected BCVA loss of more than 5 letters from day 7 postop	
Solomon 1995	6 months	Days 21 to 60, MO = positive angiography and visual acuity <= 20/40			Yes	Fluorescein angiography using classification***		Snellen acuity but not reported by treatment group	
Tauber 2006	30 days (3 months mentioned but not reported)			Reported but no mean/SD					Proportion with > 10% increase in retinal thickness
Ticly 2014	5 weeks			Final value	Yes	Fluorescein angiography using Miyake 1977 classification		LogMAR	
Tunc 1999	2 months					Fluorescein angiography 0 no leakage (CME absent), 1 oedema less than			

Table 6. Outcomes (*Continued*)

						perifoveal, 2 mild perifoveal oedema, 3 moderate perifoveal oedema (approx. 1 disc diameter), 4 severe perifoveal oedema plus drop of 1 line of Snellen acuity since second postoperative week defined as "clinically significant"			
Tzelikis 2015	12 weeks			Final value	Yes			LogMAR, final value (at 30 days only)	
Umer-Bloch 1983	12 weeks				Yes	Fluorescein angiography using Miyake 1977 classification		Snellen acuity only, not included in analyses	
Wang 2013	2 months	OCT-confirmed CMO with "visual impairment" (not specified cutpoint)		Final value	Yes	"CME was defined as central retinal thickness > 250 μm and the presence of intraretinal cystoid	Mean photon count values	LogMAR, final value	

Table 6. Outcomes (*Continued*)

						space beneath the foveal, with the diagnosis confirmed by the same retinal specialist"			
Wittpenn 2008	4 weeks	OCT-confirmed CMO with visual acuity < 6/9			Yes	Clinical and OCT-based			
Yannuzzi 1981	1 year	CMO on fluorescein angiography with visual acuity < 6/60			Yes	Fluorescein angiography, evidence but not defined			
Yavas 2007	3 months					"Slight fluorescein leakage into the cystic space without enclosing the entire central fovea or complete fluorescein accumulation in the cystic space was diagnosed as angiographic CME"		LogMAR, final value	
Yung 2007	12 weeks								

Table 6. Outcomes (*Continued*)

Zaczek 2014	6 weeks				Yes	OCT-verified but not defined	Mean anterior chamber flare reported in figure but no SD	LogMAR, final value	Change in total macular volume
Zhang 2008	1 month					OCT-verified but not defined	Tyn granule +		

BCVA: best corrected visual acuity
CME: cystoid macular oedema (edema)
CMO: cystoid macular oedema
COMTOL: Comparison of Ophthalmic Medications for Tolerability (questionnaire)
MO: macular oedema
OCT: ocular coherence tomography
SD: standard deviation

Table 7. Adverse effects

Study	Follow-up	Number of people followed up	Adverse effects
Almeida 2008	1 month	74	Quote: "There were 3 dropouts in the treatment group related to ketorolac corneal toxicity, most notably pain attributed to the drops."
Almeida 2012	1 month	162	Quote: "One patient in the ketorolac group was hospitalized with a cardiovascular event and could not complete the follow-up. Finally, 1 patient on nepafenac had side effects of ocular redness and irritation and could not continue with the study."
Asano 2008	8 weeks	142	2 "complications" not specified.
Brown 1996	1 month	NR	Adverse effects not reported.

Table 7. Adverse effects (*Continued*)

Cervantes-Coste 2009	6 weeks	60	Quote: "There were no serious treatment-related adverse events or toxicity related to the use of nepafenac 0.1%."
Chatziralli 2011	6 weeks	138	Quote: "All patients reported pain and ocular discomfort lower than 1/10 on the visual analog scale at all time points."
Donnenfeld 2006	2 weeks	100	Quote: "Use of ketorolac 0.4% for 1 or 3 days provided decreased levels of patient discomfort intraoperatively and postoperatively. Intraoperatively, 3 days of ketorolac 0.4% provided significantly lower discomfort scores than with 1-hour and placebo dosing (P < 0.001). One day of ketorolac 0.4% also provided significantly reduced intraoperative discomfort scores than with 1-hour dosing (P = 0.001) and placebo dosing (P < 0.001). Postoperatively, 3 days of ketorolac 0.4% provided significantly lower discomfort scores than 1-hour dosing or control dosing (P < 0.001) (Figure 5). In addition, patients randomised to 1 or 3 days of ketorolac 0.4% were significantly less likely to require additional intravenous anesthesia (8% in each group) than patients in the control group (40%) (P = 0.008). Twenty percent of patients in the 1-hour group required additional anesthesia for pain control."
Elsawy 2013	12 weeks	86	Adverse effects not reported.
Endo 2010	6 weeks	62	Quote: "No adverse events were noted in either group."
Italian Diclofenac Study Group 1997	140 days	229	Quote: "No major adverse effects were noted in either group.

Table 7. Adverse effects (*Continued*)

			" "Subjective tolerance of the two treatments was good and remained similar throughout the study, although a trend towards increased burning was seen in the diclofenac group."
Jung 2015	1 month	91	Quote: "There were no adverse events except for a mild burning sensation in one patient in the ketorolac group; the symptom was tolerable and did not lead to discontinuation of the medication."
Kraff 1982	between 2.5 and 12 months	492	Quote: "There were no complications that could be ascribed to the use of topical indomethacin other than minor stinging and burning noted by the patients."
Li 2011	1 month	217	Adverse effects not reported.
Mathys 2010	2 months	79	Quote: "There were no adverse events reported by patients using nepafenac."
Miyake 2007	5 weeks	50	Adverse effects not reported.
Miyake 2011	5 weeks	55	NSAIDs: 6 adverse effects: decreased lacrimation, conjunctivitis allergic, abnormal sensation in eye, vomiting (2), constipation Steroid group: 9 adverse effects: decreased lacrimation, conjunctivitis allergic, retinal haemorrhage, keratoconjunctivitis sicca, chorioretinopathy, influenza, insomnia, diarrhoea, humeral fracture
Miyanaga 2009	2 months	72	Adverse effects not reported.
Moschos 2012	1 month	79	Adverse effects not reported.
Quentin 1989	180 days	112	Quote: "Diclofenac group: two patients were feeling burning after application of eye drops

Table 7. Adverse effects (*Continued*)

			during the stationary care, for placebo: none. In both groups burning was reported later on in the examinations."
Rossetti 1996	6 months	88	Quote: "Treatment regimens were well tolerated with no evidence of relevant side effects."
Singh 2012	90 days	251	Quote: "No patient deaths were reported during the study. Overall, 13 patients reported other serious adverse events, none of which were related to treatment. Three of the serious adverse events reported in the vehicle group (cardiac failure congestive, coronary artery occlusion, and pancreatitis) led to patient discontinuation; no other serious adverse events led to discontinuation in either treatment group. Separate from the three patients who discontinued due to serious adverse events, four other patients discontinued study participation due to nonserious adverse events. Of these nonserious events, two reported instances of punctate keratitis (one in each treatment group) were assessed as being related to the study drugs. No instances of targeted adverse events (defined as corneal erosions) were reported during the study Two reports of punctate keratitis and a single report of corneal epithelium defect were assessed as being related to treatment with nepafenac. A single report of punctate keratitis was assessed as being related to treatment with vehicle. No other ocular or nonocular adverse events reported in the study were assessed as being related to the

Table 7. Adverse effects (*Continued*)

			study drugs In both treatment groups, corneal staining and intraocular pressure were each generally similar at the presurgical baseline and at the day 90 visit (or early exit). Additionally, no safety issues or trends were identified based upon changes from baseline in fundus parameters (retina/macula/choroid and optic nerve) and ocular signs (inflammatory cells, aqueous flare, corneal oedema, and bulbar conjunctival injection). The study results indicate no new clinically relevant risks associated with increasing the dosing of nepafenac from 14 days to 90 days, even in the higher-risk diabetic patient population."
Solomon 1995	6 months	364	Quote: "During the study, the mean severity of foreign-body sensation, pain, photophobia, and tearing did not become more than mild (1 +) in any treatment group. This was also true of burning and stinging following treatment instillation (Figure 4). The severity of burning and stinging was significantly greater in the flurbiprofen group on days 4-20 and 21-60 and in the indomethacin group on days 1-3, 4-20, 21-60, and 61-120 than in the vehicle group. At day 1-3, moderate to severe burning and stinging were reported by 7.0% (16/230) of the patients treated with flurbiprofen, 9.7% (23/237) of the patients treated with indomethacin, and 3.1% (7/224) of the patients treated with vehicle."
Tauber 2006	30 days (3 months mentioned but not reported)	32	Adverse effects not reported.

Table 7. Adverse effects (*Continued*)

Ticly 2014	5 weeks	81	One patient withdrew because of burning.
Tunc 1999	2 months	75	Adverse effects not reported.
Tzelikis 2015	1 month	126	Quote: "There were no adverse side effects in either group."
Umer-Bloch 1983	12 weeks	73	Quote from translation: "40% reported a short burning after using indomethacin eye drops, only rare in patients of the placebo group. One patient had 6 weeks after treatment an allergic blepharitis due to indomethacin. Long-term: 52 patients were followed for 6 months and 34 patients one year. 4 patients with indomethacin had visual acuity reduction because of a clinically new cystoid edema; 2 of these patients had spontaneous healing after 4-6 weeks, the other 2 edema cases did not resolve. 2 patients had a new senile macula pathology, and 2 patients had a retinal detachment due to aphakia. Placebo: 2 patients still had an edema after 12 weeks, while one patient developed a new edema later."
Wang 2013	2 months	167	Quote: "No drug-related adverse events were identified."
Wittpenn 2008	4 weeks	478	Quote: "The most commonly reported adverse events (investigator self-report) in the ketorolac/steroid group were burning/stinging/tearing (4/268). Transient elevations in intraocular pressure (IOP) were the most commonly reported adverse event in the steroid group (3/278). There were two serious adverse events, both in the steroid group: one patient

Table 7. Adverse effects (*Continued*)

			developed endophthalmitis and one patient died (cause determined to be unrelated to the study medication)."
Yannuzzi 1981	1 year	231	Adverse effects not reported.
Yavas 2007	3 months	179	Adverse effects not reported.
Yung 2007	12 weeks	37	Adverse effects not reported.
Zaczek 2014	6 weeks	152	Quote: "Mild to moderate punctuate epithelial defects of the cornea were found in both groups 3 weeks after treatment. Statistically significantly more patients in the nepafenac group than in the control group had corneal fluorescein staining (20 [26.7%] versus 8 [10.4%]) (PZ. 0119). Headache was reported by 3 patients (4.0%) in the nepafenac group and 2 patients (2.6%) in the control group (PZ.9750). No other systemic or local untoward effects were recorded during 3 weeks of treatment in either study group. "
Zhang 2008	1 month	220	Adverse effects not reported.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Macular Edema, Cystoid
#2 macula* near/3 (edema* or odema*)
#3 (cme or cmo)
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Anti-Inflammatory Agents, Non-Steroidal
#6 nsaid*
#7 nonsteroidal anti-inflammator*
#8 non-steroidal anti-inflammator*
#9 MeSH descriptor Diclofenac
#10 diclofenac* OR fenoprofen* OR flurbiprofen*
#11 MeSH descriptor Indomethacin
#12 indometacin*
#13 MeSH descriptor Ketoprofen
#14 ketoprofen*
#15 ketorolac
#16 piroxicam
#17 (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
#18 (#4 AND #17)

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 macular edema cystoid/
14. exp macula lutea/
15. (macula$ adj3 oedema).tw.
16. (macula$ adj3 edema).tw.
17. (CME or CMO).tw.
18. or/13-17
19. exp anti inflammatory agents non steroidal/
20. nsaid$.tw.
21. nonsteroidal anti-inflammator$.tw.
22. non-steroidal anti-inflammator$.tw.
23. exp diclofenac/
24. diclofenac$.tw.
25. fenoprofen$.tw.
26. flurbiprofen$.tw.
27. exp indometacin/
28. indometacin$.tw.

29. exp ketoprofen/
30. ketoprofen$.tw.
31. ketorolac$.tw.
32. piroxicam$.tw.
33. or/19-32
34. 18 and 33
35. 12 and 34

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 propspectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp retina macula cystoid edema/
34. exp eye edema/
35. exp retina macula lutea/
36. (macula$ adj3 oedema).tw.
37. (macula$ adj3 edema).tw.
38. (CME or CMO).tw.
39. or/33-38
40. exp nonsteroidal antiinflammatory agent/
41. nsaid$.tw.

42. nonsteroidal anti-inflammator$.tw.
43. non-steroidal anti-inflammator$.tw.
44. exp diclofenac/
45. diclofenac$.tw.
46. fenoprofen$.tw.
47. flurbiprofen$.tw.
48. exp indometacin/
49. indometacin$.tw.
50. exp ketoprofen/
51. ketoprofen$.tw.
52. ketorolac$.tw.
53. exp piroxicam/
54. piroxicam$.tw.
55. or/40-54
56. 39 and 55
57. 32 and 56

Appendix 4. LILACS search strategy

Anti-Inflammatory Agents, Non-Steroidal [Subject descriptor] or nonsteroidal antiinflammator$ or nonsteroidal anti inflammator$ or non steroidal anti inflammator$ or NSAID$ and macula$ edema or macula$ oedema or CMO or CME

Appendix 5. ISRCTN search strategy

"(Condition: macular edema OR macular oedema AND Interventions: NSAID OR nonsteroidal anti-inflammatory OR non-steroidal anti-inflammatory)"

Appendix 6. ClinicalTrials.gov search strategy

macular edema OR macular oedema OR CMO OR CME | NSAID OR nonsteroidal anti-inflammatory OR non-steroidal anti-inflammatory

Appendix 7. WHO ICTRP search strategy

macular edema OR macular oedema OR CMO OR CME = Condition AND NSAID OR nonsteroidal anti-inflammatory OR non-steroidal anti-inflammatory = Intervention

Appendix 8. Data for characteristics of included studies

Mandatory items		**Optional items**
Methods		
Study design	· **Parallel group RCT** *i.e. people randomised to treatment* · **Within-person RCT** *i.e. eyes randomised*	Exclusions after randomisation Losses to follow-up Number randomised/analysed

(*Continued*)

	to treatment · **Cluster-RCT** *i.e. communities randomised to treatment* · **Cross-over RCT** · Other, specify	How were missing data handled? *e.g. available case analysis, imputation methods* Reported power calculation (Y/N*), if yes, sample size and power* Unusual study design/issues
Eyes *or* unit of randomisation/ unit of analysis	· **One eye included in study**, *specify how eye selected* · **Two eyes included in study, both eyes received same treatment**, *briefly specify how analysed (best/worst/average/both and adjusted for within-person correlation/both and not adjusted for within-person correlation) and specify if mixture one eye and two eyes* · **Two eyes included in study, eyes received different treatments,** *specify if correct pair-matched analysis done*	
Participants		
Country		Setting Ethnic group Equivalence of baseline characteristics (Y/
Total number of participants	*This information should be collected for total study population recruited into the study. If these data are only reported for the people who were followed up, please indicate.*	
Number (%) of men and women		Number (%) of men and women
Average age and age range		Average age and age range
Inclusion criteria		
Exclusion criteria		
Interventions		
Intervention (n=) Comparator (n=) ***See MECIR 65 and 70***	· Number of people randomised to this group · Drug (or intervention) name · Dose · Frequency · Route of administration	
Outcomes		
Primary and secondary outcomes *as defined in study reports* ***See MECIR R70***	List outcomes Adverse effects reported (Y/N) Length of follow-up and intervals at which outcomes assessed	Planned/actual length of follow-up

(*Continued*)

Notes		
Date conducted	Specify dates of recruitment of participants mm/yr to mm/yr	Full study name: *(if applicable)* Reported subgroup analyses (Y/N) Were trial investigators contacted?
Sources of funding		
Declaration of interest ***See MECIR 69***		

HISTORY

Protocol first published: Issue 3, 2007

Review first published: Issue 11, 2016

Date	**Event**	**Description**
10 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

- Conceiving the review: Cochrane Eyes and Vision (CEV)
- Designing the review: JE
- Co-ordinating the review: JE
- Data collection for the review
    - designing search strategies: CEVG Information Specialist
    - undertaking electronic searches: CEVG Information Specialist
    - screening search results: BL, CL, DL
    - organising retrieval of papers: CEVG Information Specialist
    - screening retrieved papers against inclusion criteria: BL, CL, DL
    - appraising quality of papers: BL, CL, DL, JE
    - extracting data from papers: BL, CL, DL, JE
    - writing to authors of papers for additional information: BL, JE
    - providing additional data about papers: BL, JE
    - obtaining and screening data on unpublished studies: JE, BL

- Data management for the review
    - entering data into RevMan 5: JE
    - analysis of data: JE, CB
- Interpretation of data
    - providing a methodological perspective: JE, CB, RW
    - providing a clinical perspective: BL, CL, DL, RW
    - providing a policy perspective: RW
- Writing the review: BL, CL, DL, JE, RW
- Providing general advice on the review: RW

DECLARATIONS OF INTEREST

JE: None known

BL: Noneknown

CL: None known

DL: None known

CB: None known

RW: None known.

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- Cochrane Incentive Scheme awarded in 2015.

The views expressed in this publication are those of the authors and not necessarily those of the NIHR, NHS, or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol we had planned to contact pharmaceutical companies for more information (Goh 2007). We did not do this because since the protocol was written, the role of clinical trial registries have meant that it is much easier to identify potentially unpublished trials.

We had planned to use confidence intervals for the I^2 value, but as this is not routinely implemented in RevMan 5 as yet, we have not done this. We felt the extra effort required to analyse the data in a software package that could provide these confidence intervals, such as Stata, was not worth it.

We added some additional outcomes as a result of our collaboration with the National Institute for Health and Care Excellence (NICE). These are clearly identified in the text. We have clarified our definition of macular oedema to include all 3 levels of the Miyake classification and whether or not cystic spaces are detectable on imaging which we have termed simply macular oedema (MO). Cystoid has been removed from the title.

NOTES

The protocol for this review question was first published in 2007 (Goh 2007). The original review team were unable to complete the review and therefore a new review team was found. The latest protocol for this review was published in 2011 (Abeysiri 2011).

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Topical; Anti-Inflammatory Agents, Non-Steroidal [adverse effects; *therapeutic use]; Cataract Extraction [*adverse effects]; Macular Edema [etiology; *prevention & control]; Postoperative Complications [*prevention & control]; Randomized Controlled Trials as Topic; Steroids [therapeutic use]

MeSH check words

Aged; Humans