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TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	4
METHODS	4
RESULTS	6
Figure 1.	7
DISCUSSION	7
AUTHORS' CONCLUSIONS	8
ACKNOWLEDGEMENTS	8
REFERENCES	9
APPENDICES	11
CONTRIBUTIONS OF AUTHORS	13
DECLARATIONS OF INTEREST	14
SOURCES OF SUPPORT	14
INDEX TERMS	14

[Intervention Review]

Topical non-steroidal anti-inflammatory agents for diabetic cystoid macular oedema

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ABSTRACT

Background

Diabetic cystoid macular oedema (CMO) is a condition which involves fluid accumulation in the inner portion of the retina. It often follows changes in retinal blood vessels which enhance the fluid to come out of vessels. Although it may be asymptomatic, symptoms are primarily painless loss of central vision, often with the complaint of seeing black spots in front of the eye.

It is reported that CMO may resolve spontaneously, or fluctuate for months, before causing loss of vision. If left untreated or undiagnosed, progression of CMO may lead to permanent visual loss.

It has been noted that patients with diabetic retinopathy have elevated inflammatory markers, and therefore it is likely that inflammation aids in the progression of vascular disease in these patients. Several topical non-steroidal anti-inflammatory drugs (NSAIDs) such as ketorolac 0.5%, bromfenac 0.09%, and nepafenac 0.1%, have therefore also been used topically to treat chronic diabetic CMO. Hence this review was conducted to find out the effects of topical NSAIDs in diabetic CMO.

Objectives

To assess the effects of topical non-steroidal anti-inflammatory drugs (NSAIDs) for diabetic cystoid macular oedema (CMO).

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (2014, Issue 12), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to January 2015), EMBASE (January 1980 to January 2015), Latin American and Caribbean Health Sciences Literature Database (LILACS) (January 1982 to January 2015), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov) and the 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 12 January 2015.

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs investigating the effects of topically applied NSAIDs in the treatment of people with diabetic CMO aged 18 years of age or over.

Data collection and analysis

Two review authors independently assessed trial eligibility and screened all available titles and abstracts for inclusion. There were no discrepancies and we did not have to contact trial investigators for missing data.

Main results

We did not identify any RCTs matching the inclusion criteria for this review.

Authors' conclusions

The review did not identify any RCTs investigating the effects of topical NSAIDs in the treatment of diabetic CMO. Most of the studies identified through the electronic searches had been conducted to analyse the effect of topical NSAIDs for pseudophakic CMO. In the absence of high quality evidence, clinicians need to use their clinical judgement and other low level evidence, such as observational non-randomised trials, to decide whether to use topical NSAIDs in cases of diabetic CMO.

More research is needed to better understand the cause of this condition and its pathophysiology. This systematic review has identified the need for well designed, adequately powered RCTs to assess possible beneficial and adverse effects of topical NSAIDs in people with diabetic CMO. Future trials should aim to include a large sample size with an adequate follow-up period of up to one year.

PLAIN LANGUAGE SUMMARY

Topical non-steroidal anti-inflammatory agents for diabetic cystoid macular oedema

Review question

We reviewed the evidence about the effect of non-steroidal anti-inflammatory drugs for diabetic cystoid macular oedema.

Background

Diabetic retinopathy is a frequent cause of blindness in adults aged between 20 and 74 years. The major cause of vision impairment in those with diabetic retinopathy is the accumulation of fluid in the central part of the retina (macula) known as cystoid macular oedema (CMO). CMO is the chronic and diffuse variety of diabetic macular oedema (DMO). The use of topical anti-inflammatory agents has been suggested as a potential treatment for diabetic CMO.

We aimed to review randomised controlled trials (RCTs) and quasi-RCTs (these are clinical research studies, which give good quality evidence on the effects of interventions) that investigated the effects of various topically applied non-steroidal anti-inflammatory drugs (NSAIDs) in treating diabetic CMO, and evaluate whether significant benefits have occurred with topical NSAIDs.

We reviewed the evidence on the effect of locally applied NSAID eye preparations on restoring vision in people with diabetic CMO. Although various topical NSAIDs have been used to treat diabetic CMO, namely bromfenac 0.09%, nepafenac 0.1% and ketorolac 0.5%, we did not find any RCTs or quasi-RCTs that were eligible for this review. We also found that most of the studies identified through the electronic searches had been conducted to analyse the effect of topical NSAIDs for pseudophakic CMO.

Greater research is required to understand the effects of topical NSAIDs on diabetic CMO. We would recommend a RCT to assess the effects of topical NSAIDs in patients with diabetic CMO. The trial would need to have a follow-up of at least one year, and include a large sample size and a robust design in order to assess any potential long-term beneficial or adverse effects of locally applied NSAIDs.

Search date

The evidence is current to January 2015.

BACKGROUND

Description of the condition

Diabetes mellitus, especially Type 2, is escalating (Mokdad 2001) and is estimated to reach epidemic proportions around the world in the next 25 years (Bonow 2004). The prevalence of diabetes in adults worldwide was estimated at 4.0% in 1995 and is expected to rise to 5.4% by the year 2025 (Cockram 2000; King 1998). Diabetic retinopathy is a known complication of diabetes mellitus (Xiao-Ling 2006), and is increasingly becoming a major cause of blindness throughout the world (Congdon 2003; Viswanath 2003).

Cystoid macular oedema (CMO) is a condition where accumulation of fluid occurs in the central part of the retina, largely due to capillary leakage. Although the most common cause of CMO is cataract surgery and other intraocular surgeries, it has also been observed in various other ocular conditions such as diabetic retinopathy, age-related macular degeneration, uveitis, and eye injury etc. In diabetic CMO, the cystoid changes usually occur in cases of diffuse and chronic diabetic macular oedema (DMO) (Rotsos 2008).

Theories of the pathogenesis of CMO have looked at mechanical factors, such as tractional forces on the macula and disruption of the vitreoretinal interface (Rotsos 2008). However, the most accepted theory to date is vascular leakage and retinal oedema, initiated by the diffusion of mediators like prostaglandins being released in the eye (Scholl 2010). This theory is supported by evidence that cyclo-oxygenase inhibitors reduce the incidence of angiographic CMO. Although natural history studies of pseudophakic CMO have shown that the majority of cases resolve spontaneously, one natural history study on diabetic CMO has shown the persistence of cystoid spaces, resulting in a severe decrease in visual acuity (Coscas 1984).

It is difficult to know the true incidence of CMO. Whilst subtle CMO is difficult to identify clinically, there may also be other factors that affect the accuracy of incidence estimates. New CMO is normally reported through the surgeon's findings or via fluorescein angiography and optical coherence tomography.

Although CMO is often symptomatic in terms of visual impairment in either eye, it may be asymptomatic in some cases. It is reported that CMO may resolve spontaneously, or fluctuate for months before causing severe loss of vision, which often results in diminution of visual acuity to 20/200 level (Massin-Korobelnik 1994). Fundoscopy usually shows an altered foveal reflex with a honeycomb appearance of the macula. In cases where the diagnosis of CMO is unclear, fundus fluorescein angiography may be used. The classical angiography picture is a 'flower petal' appearance at the macula. The amount of macular oedema can also be detected by a non-invasive procedure called optical coherence tomography.

Various treatment options are available for diabetic CMO. The mainstays of treatment are grid photocoagulation (ETDRS 1987), intravitreal steroids (Grover 2008), vitrectomy (Otani 2002), and the most recent, intravitreal vascular endothelial growth factor (Haritoglou 2006).

Description of the intervention

Medical therapies for diabetic CMO have included two broad classes of agents: anti-inflammatory drugs and agents with molecular targets (Boscia 2010). It has been found that patients with diabetic retinopathy have elevated inflammatory markers. Thus it is likely that inflammation aids in the progression of vascular disease in these patients (Ke 2000; Meleth 2005). Several topical non-steroidal anti-inflammatory drugs (NSAIDs) such as ketorolac 0.5%, bromfenac 0.09%, and nepafenac 0.1%, have also been used to treat chronic diabetic CMO. A Cochrane systematic review found two trials with topical ketorolac 0.5% ophthalmic solution that had a positive effect for treating chronic CMO following cataract surgery, and two trials that revealed no significant difference between the intervention and control groups (Sivaprasad 2005).

How the intervention might work

Topical NSAIDs are commonly prescribed in ophthalmic practice for their anti-inflammatory property. In diabetic CMO, there is extracellular fluid accumulation and retinal oedema which is secondary to disruption of the blood retinal barrier (Gardner 2002). Studies have also demonstrated an association between CMO and inflammation mediated by prostaglandins (Bazan 1990; Miyake 2002; Scholl 2010). In the eye, prostaglandins are synthesised in the ciliary body and iris, causing vasodilatation and increasing vascular permeability with disruption of the blood-ocular barrier with leukocyte migration, which results in oedema formation (Miyake 2002).

NSAIDs act as potent inhibitors for cyclo-oxygenase enzymes, an active component of the inflammatory process involved in prostaglandin synthesis. When administered topically, NSAIDs achieve therapeutic levels in the aqueous humour, and are capable of a reduction in the synthesis of prostaglandins in the ciliary body and iris. More frequent administration of topical NSAIDs with longer duration of treatment leads to higher aqueous levels (Bucci 2007). Three topical NSAIDs, ketorolac 0.4%, bromfenac 0.09% and nepafenac 0.1% were proven to penetrate into the vitreous cavity, and ketorolac lowers the vitreous level of Prostaglandin E2 (PGE2) (Heier 2009) which is reportedly associated with vasodilatation and partial disruption of the blood-ocular barrier (Quaranta 2013). It has been suggested that vasogenesis as well as vasogenic macular oedema can also be strategically controlled by administration of anti-inflammatory drugs such as NSAIDs (Boscia 2010).

Why it is important to do this review

Diabetic retinopathy is found to be the most frequent cause of new cases of blindness in adults aged 20 to 74 years (Klein 1984). Diabetic CMO is one of the factors for severe vision impairment in patients with diabetic retinopathy. DMO is the leading cause of visual impairment that occurs with diabetic retinopathy (Girach 2007). Diabetic CMO is more commonly found where there is diffuse and chronic DMO.

As with most treatments mentioned earlier, however, there are limitations and risks, most notably their invasive nature. The use of a topical alternative would therefore be markedly safer and easier, if proven to be effective. A few studies have reported the beneficial effect of topical NSAIDs in treating diabetic CMO as well as DMO; however there is currently no available systematic appraisal of evidence of the safety and effectiveness of topical NSAIDs for cases

of diabetic CMO. A systematic review would assist in analysing the effects of topical NSAIDs in reducing or resolving diabetic CMO.

OBJECTIVES

To assess the effects of topical non-steroidal anti-inflammatory drugs (NSAIDs) for diabetic cystoid macular oedema (CMO).

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include all randomised controlled trials (RCTs). We also planned to include quasi-RCTs if evidence of effects (benefits or harms) could not be adequately studied in RCTs and only if there was sufficient evidence that intervention and control groups were similar at baseline.

Types of participants

We did not take into consideration gender and race when selecting trials, although participants had to be over the age of 18 years. We included participants that had diabetic CMO diagnosed clinically. We did not exclude from this review participants who were non-responsive to previous treatment (i.e. photocoagulation).

Types of interventions

We planned to include trials where topical NSAIDs were compared to placebo, no treatment, and other modalities of treatment.

Types of outcome measures

Primary outcomes

1. The primary outcome for this review was 2 or more lines improvement of visual acuity from baseline (Early Treatment Diabetic Retinopathy Study (ETDRS), Snellen or LogMAR equivalent) at three months of treatment.

Secondary outcomes

1. Proportion of participants showing improvement in central retinal thickness, measured with optical coherence tomography after three months of treatment, as a continuous outcome.
2. Proportion of participants showing persistence of subretinal fluid with optical coherence tomography after three months of treatment as a dichotomous outcome.
3. Proportion of participants showing improvement in fundus fluorescein angiography findings after three months of treatment. (Improvement is defined by decreased leakage in fundus fluorescein angiography).
4. Quality of life: we planned to summarise the data on quality of life by any validated measure (such as National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) and Impact of Visual Impairment (IVI) Questionnaire) when found to be reported in the included studies.
5. Adverse outcomes: we planned to tabulate all adverse effects related to topical application of NSAIDs for the treatment of diabetic CMO that are found to be reported in the included studies.

Search methods for identification of studies

Electronic searches

We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (2014, Issue 12), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to January 2015), EMBASE (January 1980 to January 2015), Latin American and Caribbean Health Sciences Literature Database (LILACS) (January 1982 to January 2015), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictip/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 12 January 2015.

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 ([Appendix 7](#)).

Searching other resources

We handsearched the International Congress of Ophthalmology from 1990 onwards until the last congress in 2012 to identify unpublished studies. We contacted organisations and researchers in the field of ophthalmology, and pharmaceutical companies for information on current trials. We also checked the reference lists of all trials identified by the above methods.

Data collection and analysis

Selection of studies

Two review authors (SS, KT) independently assessed trial eligibility and screened all available titles and abstracts for inclusion. If relevant data from the abstract were difficult to ascertain, the full-text of the report was retrieved. Two review authors (SS, KT) assessed the eligibility criteria independently by filling-in the eligibility form that was designed in accordance with the inclusion criteria. The review authors were unmasked to the trial authors, institutions and trial results during their assessments. If a disagreement occurred, they were solved by discussion, or if required, a third review author (AH) was asked to express his view.

As no trials met our inclusion, we will follow the steps below for future updates.

Data extraction and management

Two review authors (SS, KT) planned to independently extract data for primary and secondary outcomes onto paper data collection forms developed by the Cochrane Eyes and Vision Group. The same two authors then planned to share the responsibility of entering the data into Review Manager 5 ([RevMan 2014](#)) and a third author (AN) planned to check for errors and inconsistencies. We planned to resolve any differences in data extraction by discussion and consensus.

We planned to use a standard data extraction form which will include at least the following items.

1. Method: duration, way of randomisation, allocation concealment method, masking, country, and setting.

2. Participants: type of sampling, number in comparison group, age, sex, similarity of group at base line, and losses to follow-up with reason.
3. Interventions: placebo will be included, interventions (dose, route and duration), comparison intervention (dose, route and duration), and co-medication (dose, route and duration).
4. Outcomes: outcomes specified above, any other outcomes assessed, times of assessment, and length of follow-up.
5. Notes: published or unpublished data, title, authors, source, contact address, language of publication, year of publication, and funding sources if any.

Assessment of risk of bias in included studies

Two review authors (AB, AN) planned to independently assess the risk of bias of the included studies by using the criteria outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We planned to resolve any disagreements by discussion or by the intervention of a third review author (SN).

We planned to assess the following five components for each of the trials: random sequence generation (selection bias); allocation concealment (selection bias); masking (blinding) of participants and personnel (performance bias), and masking of outcome assessment (detection bias); incomplete outcome data (attrition bias through withdrawals, drop outs and protocol deviations); and selective reporting bias. We also planned to assess other sources of bias as reported in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), such as bias related to the specific study design, early stoppage of trials, extreme baseline imbalance or whether the study appeared to have been fraudulent. For each of these components, we planned to assign one of the following risk of bias judgements: 'low risk' of bias, 'high risk' of bias, or 'unclear risk' for uncertain risk of bias. We planned to record the results in the standard table in Review Manager 5 (RevMan 2014), and to summarise the findings in a 'Risk of bias' table or graph.

Measures of treatment effect

For data analysis, we planned to follow the guidelines set out in Chapter 9 of the *Cochrane Handbook for Systematic Review of Interventions* (Deeks 2011).

For dichotomous data such as improvement of 2 or more Snellen lines, persistence of subretinal fluid detected by optical coherence tomography, improvement in fundus fluorescein angiography and occurrence of adverse effects, we planned to present the results using risk ratios (RRs) and their 95% confidence intervals (CIs).

For continuous outcomes such as central retinal thickness and quality of life we planned to calculate mean difference (MD) if the outcomes were measured by the same scales within the included studies. If the same outcomes were measured by different scales, we planned to use standard mean difference (SMD) with 95% CIs.

Unit of analysis issues

In ophthalmic RCTs, the unit of analysis can be either the participant or the eye. If the unit of analysis is the eye, it can be one eye, two eyes or mixed. In two-eyed studies, if both eyes received the same treatment, we considered these studies as clustered, and if both eyes received different treatments, they would be considered as paired. For each trial included, we planned to

document the unit of analysis and study design. If included studies used different methods, we planned to estimate the treatment effect at the study level and perform meta-analysis by using the inverse variance method.

Dealing with missing data

Where data are missing due to participant drop out, we planned to conduct a primary analysis based on participants with complete data. We consider that missing outcomes will not be a problem if loss to follow-up is documented and judged to be unrelated to outcomes in both study arms, as per Chapter 16 of the *Cochrane Handbook for Systematic Review of Interventions* (Higgins 2011b). We planned to get full reports from authors where studies are either published in abstract form or presented at meetings. We planned to contact the primary investigator in case of missing data or unclear information in the study reports. We also planned to consider that missing outcome data are not a problem if the causes are well documented. However, if the causes of missing data are not available, we planned to document the possible effects of the missing participants through a sensitivity analysis.

Assessment of heterogeneity

We planned to use the Chi² test to assess statistical heterogeneity and considered $P < 0.1$ as statistically significant. To quantify the statistical heterogeneity, we planned to use forest plots and the I² statistic. We planned to use the following guidelines for interpreting I² values: 0% to 40% as insignificant heterogeneity, 30% to 60% as moderate heterogeneity, 50% to 90% as substantial heterogeneity, and 75% to 100% as considerable heterogeneity (Deeks 2011). We also planned to assess clinical and methodological heterogeneity by examining the characteristics and methodology section of individual studies.

Assessment of reporting biases

Three review authors (SS, KT, AH) carried out comprehensive searches to minimise publication and reporting biases, and they planned to consider the likelihood of these biases. Within studies, we planned to consider selective outcome reporting as part of the risk of bias assessment. We planned to compare the 'Methods' section of the fully published paper to the 'Results' section to ensure that all of the outcomes which were measured, were reported. We planned to assess possible publication bias by using funnel plots to explore the relationship between effect size and study size. We also planned to look at funnel plots only where we have sufficient trials i.e. 10 trials or more. We would visually examine them for symmetry, with greater symmetry indicating a lower risk of reporting bias.

Data synthesis

We planned to carry out statistical analysis using Review Manager 5 (RevMan 2014). If there are less than three studies, we would use a fixed-effect model. If there is minimal statistical heterogeneity and if there is minimal clinical heterogeneity between the trials, we planned to combine the results in a meta-analysis using a random-effects model. If there is considerable heterogeneity (I² statistic of 50% or more), we will discuss the results in narrative and tabulated form only. For identifying heterogeneity we would not only rely on the statistical significance of a Chi² test, but also examine the results of the forest plot of the study. We planned to convert Early Treatment Diabetic Retinopathy Study (ETDRS) letter scores to

logMar for calculations and then use them in the meta-analysis. If we find studies in which Snellen (decimal) visual acuity is measured by non-ETDRS or non-logarithmic charts, we would only extract data if calculations are based on logMar transformed data and then transformed back to decimals for reporting. If we find studies in which means and standard deviations (SDs) are computed using decimal visual acuity, we would not use them in the meta-analysis but planned to summarise their results in the discussion.

Subgroup analysis and investigation of heterogeneity

We did not perform any subgroup analyses in this review.

Sensitivity analysis

We planned to carry out sensitivity analysis to investigate the robustness of the results regarding the various components of risk of bias. We also planned to examine the effect on the primary outcome of excluding any study judged to be at overall high risk of bias.

Summary of findings

We planned to create a ‘Summary of findings’ table using GRADEpro software (version 3.6) ([GRADEpro 2014](#)) to assess parameters such as limitations of design, inconsistency, indirectness, imprecision and publication bias. In the table we planned to include all the available outcomes reported in the included studies.

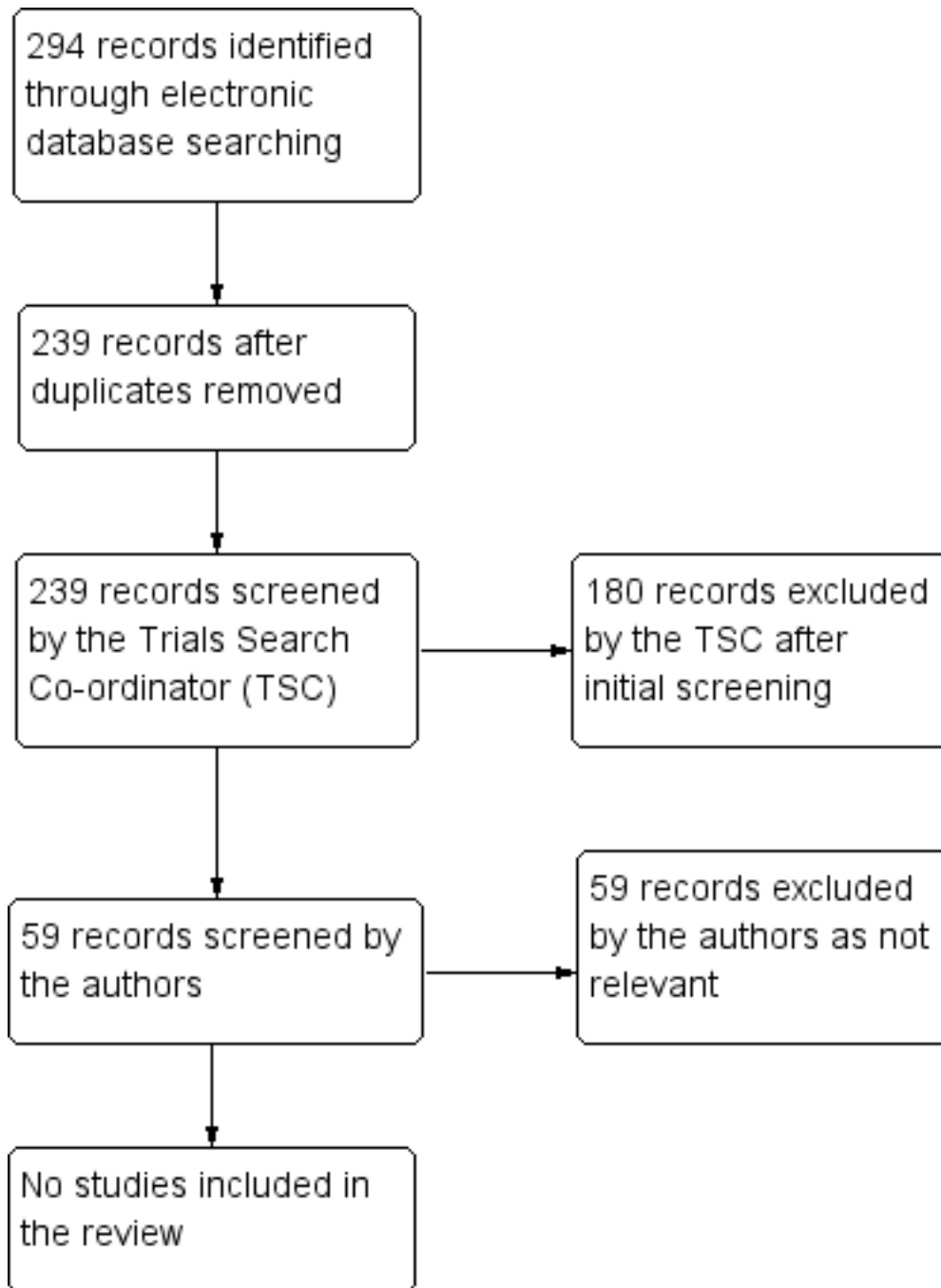
RESULTS

Description of studies

Results of the search

The electronic searches yielded a total of 294 references ([Figure 1](#)). The Trials Search Co-ordinator scanned the search results, removed 55 duplicates and then removed 180 references which were not relevant to the scope of the review. We screened the remaining 59 reports but did not identify any RCTs that met the inclusion criteria for this review.

Figure 1. Results from searching for studies for inclusion in the review



Included studies

We did not identify any RCTs that met the inclusion criteria.

Excluded studies

We did not exclude any RCTs.

Risk of bias in included studies

We did not identify any eligible trials for inclusion in the review.

Effects of interventions

The searches did not identify any RCTs, or any ongoing trials for inclusion in this review.

DISCUSSION

This review of topical non-steroidal anti-inflammatory drugs (NSAIDs) for diabetic cystoid macular oedema (CMO) failed to identify any randomised controlled trials (RCTs) or any ongoing trials for inclusion in this review. Most of the studies identified

through the electronic searches had been conducted to analyse the effect of topical NSAIDs for pseudophakic CMO.

A case series study evaluating the effects of topical nepafenac 0.1% in six eyes with diabetic macular oedema (DMO) showed that there was significant reduction in average foveal thickness from 417 μm to 267 μm , with statistically significant improvement in mean visual acuity from 0.78 logMAR to 0.67 logMAR after a mean follow-up period of 178 days (Callanan 2008).

Many studies have shown the benefits of single intravitreal injection of NSAIDs in DMO. A single dose of intravitreal diclofenac (500 $\mu\text{g}/0.1\text{ mL}$) in eyes with clinically significant macular oedema reported a prominent improvement in visual acuity (Soheilian 2010). Similar results were seen in two studies conducted in eyes with DMO refractory to laser photocoagulation (Maldonado 2011; Reis 2010) where intravitreal ketorolac (500 $\mu\text{g}/0.1\text{ mL}$ and 3000 $\mu\text{g}/0.1\text{ mL}$) were given, respectively.

Summary of main results

This review failed to identify any published trials or ongoing studies from trial registers reporting the effects and safety of topical NSAIDs for treating diabetic CMO. Although some case series studies have suggested the benefit of topical NSAIDs in the treatment of diabetic CMO, the absence of definitive RCTs suggest that it is an area where more evidence is needed to inform the scientific community as to the benefits and risks of treating diabetic CMO with topical NSAIDs.

Agreements and disagreements with other studies or reviews

Diabetic CMO, a form of chronic CMO, is a challenge observed in patients with diabetic maculopathy which results in a severe impairment in visual acuity (Coscas 1984). Unfortunately, however, there are no RCTs; suggesting that evidence is needed for or against the use of topical NSAIDs in the affected population.

A Cochrane systematic review evaluating the effects of NSAIDs for treating pseudophakic CMO reported that topical ketorolac tromethamine 0.5% had a positive effect for treating chronic pseudophakic CMO (Sivaprasad 2012). Although diabetic CMO has similar pathophysiology with that of chronic CMO following cataract surgery, this evidence cannot be used as evidence for the effects of topical NSAIDs in diabetic CMO.

AUTHORS' CONCLUSIONS

Implications for practice

We did not identify any randomised controlled trials (RCTs) of topical non-steroidal anti-inflammatory drugs (NSAIDs) in diabetic cystoid macular oedema (CMO) for inclusion in this review. There is no evidence to inform that topical NSAIDs are of benefit to people with diabetic CMO.

Implications for research

There is need for more research to better understand the cause of this condition and its pathophysiology. This systematic review has identified the need for well designed, adequately powered RCTs to assess the effects and adverse effects of topical NSAIDs in people with diabetic CMO suffering from impaired vision.

Although the literature shows that the incidence of angiographic pseudophakic CMO may be as high as 9% to 19% (Mentes 2003; Ursell 1999), and the estimated incidence of DMO is 7% of diabetic patients (Ding 2012), the exact incidence of diabetic CMO is not reported in the literature. Hence, it is difficult to calculate the sample size for future trials, but they should aim at a large sample size with adequate follow-up. Since diabetic CMO is a chronic condition, and studies evaluating the effects of topical NSAIDs reported improvements in foveal thickness and visual acuity at around four to six months (Callanan 2008; Hariprasad 2007; Warren 2010), this would suggest that a follow-up of approximately 12 months would be beneficial to prove the effects of topical NSAIDs.

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APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Macular Edema
 #2 macula* near/3 oedema
 #3 macula* near/3 edema
 #4 maculopath*
 #5 CME or CSME or CMO or CSMO
 #6 DMO or DME
 #7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)
 #8 MeSH descriptor Diabetes Mellitus
 #9 MeSH descriptor Diabetic Retinopathy
 #10 MeSH descriptor Diabetes Complications
 #11 diabet*
 #12 retinopath*
 #13 (#8 OR #9 OR #10 OR #11 OR #12)
 #14 MeSH descriptor Anti-Inflammatory Agents, Non-Steroidal
 #15 nsaid*
 #16 nonsteroidal anti-inflammator*
 #17 non-steroidal anti-inflammator*
 #18 MeSH descriptor Diclofenac
 #19 diclofenac*
 #20 fenoprofen*
 #21 flurbiprofen*
 #22 MeSH descriptor Indomethacin
 #23 indometacin*
 #24 MeSH descriptor Ketoprofen
 #25 ketoprofen*
 #26 ketorolac*
 #27 piroxicam*
 #28 bromfenac*
 #29 oxyphenbutazone*
 #30 suprofen*
 #31 (#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30)
 #32 (#7 AND #13 AND #31)

Appendix 2. MEDLINE (OvidSP) 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/
14. (macula\$ adj3 oedema).tw.
15. (macula\$ adj3 edema).tw.
16. maculopath\$.tw.

17. (CME or CSME or CMO or CSMO).tw.
18. (DMO or DME).tw.
19. or/13-18
20. exp diabetes mellitus/
21. diabetic retinopathy/
22. diabetes complications/
23. diabet\$.tw.
24. retinopath\$.tw.
25. or/20-24
26. exp anti inflammatory agents non steroidal/
27. nsaid\$.tw.
28. nonsteroidal anti-inflamator\$.tw.
29. non-steroidal anti-inflamator\$.tw.
30. exp diclofenac/
31. diclofenac\$.tw.
32. fenoprofen\$.tw.
33. flurbiprofen\$.tw.
34. exp indometacin/
35. indometacin\$.tw.
36. exp ketoprofen/
37. ketoprofen\$.tw.
38. ketorolac\$.tw.
39. piroxicam\$.tw.
40. bromfenac\$.tw.
41. oxyphenbutazone\$.tw.
42. suprofen\$.tw.
43. or/26-42
44. 19 and 25 and 43
45. 12 and 44

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

Appendix 3. EMBASE (OvidSP) search strategy

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

29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp retina macula edema/
34. (macula\$ adj3 oedema).tw.
35. (macula\$ adj3 edema).tw.
36. maculopath\$.tw.
37. (CME or CSME or CMO or CSMO).tw.
38. (DMO or DME).tw.
39. or/33-38
40. exp diabetes mellitus/
41. diabetic retinopathy/
42. diabet\$.tw.
43. retinopath\$.tw.
44. or/40-43
45. exp nonsteroidal antiinflammatory agent/
46. nsaid\$.tw.
47. nonsteroidal anti-inflamator\$.tw.
48. non-steroidal anti-inflamator\$.tw.
49. exp diclofenac/
50. diclofenac\$.tw.
51. fenoprofen\$.tw.
52. flurbiprofen\$.tw.
53. exp indometacin/
54. indometacin\$.tw.
55. exp ketoprofen/
56. ketoprofen\$.tw.
57. ketorolac\$.tw.
58. exp piroxicam/
59. piroxicam\$.tw.
60. bromfenac\$.tw.
61. nepafenac\$.tw.
62. oxyphenbutazone\$.tw.
63. suprofen\$.tw.
64. or/45-63
65. 39 and 44 and 64
66. 32 and 65

Appendix 4. LILACS search strategy

macula\$ edema or macula\$ oedema or CMO or CME and diabet\$ and nonsteroidal antiinflammator\$ or nonsteroidal anti inflammator\$ or non steroidal anti inflammator\$ or NSAID\$ or diclofenac or fenoprofen or flurbiprofen or indometacin or ketoprofen or ketorolac or piroxicam or bromfenac or nepafenac or oxyphenbutazone or suprofen

Appendix 5. ISRCTN search strategy

diabetic macular oedema

Appendix 6. ClinicalTrials.gov search strategy

Diabetic Macular Oedema AND (Non steroidal or NSAID)

Appendix 7. ICTRP search strategy

diabetic macular oedema and non steroidal

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Anti-Inflammatory Agents, Non-Steroidal [*therapeutic use]; Diabetic Retinopathy [complications] [*drug therapy]; Macular Edema [*drug therapy] [etiology]

MeSH check words

Humans