Non-steroidal anti-inflammatory agents for cystoid macular oedema following cataract surgery: a systematic review

S Sivaprasad, C Bunce, R Wormald

**Aim:** To examine the effectiveness of non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of cystoid macular oedema (CMO) following cataract surgery.

**Methods:** Systematic literature review of randomised controlled trials (RCTs) that evaluated the effects of NSAIDs in the treatment of CMO following cataract surgery was done according to the Cochrane Collaboration methodology.

**Results:** Seven trials involving a total of 266 participants were included. Four trials studied the effects of NSAIDs in chronic CMO while the other three trials examined the effect of NSAIDs in acute CMO. Little evidence of effectiveness was found for oral indomethacin and topical fenoprofen for chronic CMO in two small trials. Treatment with topical 0.5% ketorolac for chronic CMO was found to be effective in two trials. Three trials examined the effect of topical NSAIDs on acute CMO. The comparisons among these studies were of a homogeneous to include in one meta-analysis. Therefore, heterogeneous bias—that is, whether the analysis was “intention to treat.”

**Conclusion:** A positive effect of topical NSAID (0.5% ketorolac tromethamine ophthalmic solution) on chronic CMO was noted. However, there is not enough evidence to show the effectiveness of NSAIDs in acute CMO following cataract surgery.

Despite advances in cataract surgery, cystoid macular oedema (CMO) is still recognised as one of the most common causes of poor visual outcome following cataract surgery. The exact cause of CMO remains unclear. Most investigators agree that increased prostaglandin synthesis secondary to inflammation is a major aetiological factor for CMO. Topical non-steroidal anti-inflammatory agents (NSAIDs) have been used since the 1970s both preoperatively and postoperatively to prevent and treat CMO following cataract surgery.

A systematic review on the medical prophylaxis and treatment of CMO after cataract surgery was published in 1998. However, no conclusion could be safely drawn since the authors commented that many of the trials were of poor quality and may additionally be regarded as too heterogeneous to include in one meta-analysis. Therefore, uncertainty of the effectiveness of NSAIDs in the treatment of CMO persists.

The aim of this review based on Cochrane methodology is to examine the effectiveness of NSAIDs in the treatment of CMO following cataract surgery. The role of NSAIDs in the prophylaxis of CMO is not included.

**Materials and Methods**

**Study inclusion criteria and search strategy**

This review included randomised controlled trials in which NSAIDs in any form or dosage were compared to placebo, no treatment, or to another modality with the aim of treating CMO following cataract surgery in eyes that were otherwise healthy.

CMO was classified into two groups: acute CMO defined as therapeutic intervention within 4 months of onset of CMO and chronic CMO defined as persistence of clinical CMO 4 months after cataract surgery and treatment commenced after 4 months.

Trials were identified from the Cochrane Central Register of Controlled Trials, CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) on The Cochrane Library, Medline, Embase and LILACS (Latin American and Caribbean Literature on Health Sciences) using a search strategy that we have reported elsewhere. Reference lists of all identified trials and previous reviews were searched for additional trials. Key authors were identified and asked to identify additional published or unpublished trials. Additionally, manufacturers of non-steroidal anti-inflammatory drugs (Allergan, Inc (NYSE: AGN) and Novartis, Inc (Basle, Switzerland)) were contacted in order to retrieve information on relevant published or unpublished trials. We searched conference abstracts (sessions related to cataract) in ARVO 1975 to 2004 for mention of trials. Manual searches of journals were not done specifically for this review. There were no language or date restrictions in the electronic searches for trials. The searches were last updated in October 2004.

**Selection of trials**

Two reviewers independently scanned the titles, abstracts, and keywords of every record retrieved in the searches. Full articles were obtained of any trial that seemed to fit in the inclusion criteria. Four aspects of the trials were assessed. They included allocation concealment, masking of participants and researchers, detection bias, and attrition bias—that is, whether the analysis was “intention to treat.”

**Types of outcome measures**

The primary outcome measures were:

- An improvement of two or more lines in Snellen visual acuity or equivalent at end of treatment.
- Persistence of improvement in vision 1 month after discontinuation of treatment.

The secondary outcome measures were:

- Proportion of participants with improvement in leakage on fundus fluorescein angiography (FFA).
- Proportion of participants with improved contrast sensitivity.
- Quality of life.

Review Manager Software (version 4.2) was used to analyse the data.

**Abbreviations:** CMO, cystoid macular oedema; NSAIDs, non-steroidal anti-inflammatory agents; RCT, randomised controlled trial
RESULTS

Description of studies
The electronic searches found a total of 382 reports of studies. We obtained the full copy of 17 reports of trials that appeared to meet the inclusion criteria. We excluded 10 of these. In particular, all trials that used NSAIDs for prophylaxis of CMO were excluded. We included seven trials. A summary of the included studies is given in table 1.

Acute CMO
Three trials studied acute CMO, defined as treatment of CMO within 4 months of cataract surgery.

In the trial by Heier et al, outcome measures used included proportion of patients with an improvement of two or more lines in Snellen visual acuity and decreased angiographic leakage at the end of 1 month. They also noted the proportion of participants with an improvement of contrast sensitivity 1 month after discontinuation of medications. This trial showed that the combination of ketorolac and prednisolone was more effective in the management of acute CMO compared to either ketorolac or prednisolone alone.

In the study by Rho et al, the mean time taken for a two line improvement in Snellen visual acuity was 3.2 months. The three trials showed different effects of NSAIDs in the treatment of acute CMO.

In all the trials, only one case of ocular allergy has been reported and the patient discontinued the treatment. No other mention of adverse effects was found.

DISCUSSION

Acute CMO
All three randomised controlled trials assessing the effect of NSAIDs in the treatment of acute CMO were small and insufficiently powered. Spontaneous resolution and drug effect in acute CMO are hard to distinguish in these studies. Outcomes at 7 years suggest the natural history of CMO is spontaneous resolution.

The three trials showed different effects of NSAIDs in the treatment of acute CMO. This difference in effect can be explained by the following facts:

Review: Non-steroidal anti-inflammatory agents for treating cystoid macular oedema following cataract surgery
Comparison: NSAID versus placebo in chronic CMO
Outcome: Visual acuity improvement at end of treatment

Table 1 Details of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Participants</th>
<th>Interventions</th>
<th>Cataract surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burnett 1983</td>
<td>Randomised double masked.</td>
<td>Number randomised: 14</td>
<td>Topical 1% fenogrofen sodium v placebo four times daily for 8 weeks.</td>
<td>Aphakic eyes with chronic CMO.</td>
</tr>
<tr>
<td>Flach 1987</td>
<td>Randomised double masked.</td>
<td>Number randomised: 30</td>
<td>Topical 0.5% ketorolac tromethamine v placebo four times daily for 8 weeks.</td>
<td>Aphakic and pseudophakic eyes with chronic CMO.</td>
</tr>
<tr>
<td>Flach 1991</td>
<td>Randomised double masked, multicentre study.</td>
<td>Number randomised: 120 (61 to active treatment, 59 to placebo).</td>
<td>Topical 0.5% ketorolac tromethamine v placebo four times daily for 12 weeks.</td>
<td>Aphakic and pseudophakic eyes with chronic CMO.</td>
</tr>
<tr>
<td>Yannuzzi 1977</td>
<td>Randomised double masked.</td>
<td>Number randomised: 20</td>
<td>Oral indomethacin 25 mg v placebo three times a day for 6 weeks.</td>
<td>Aphakic chronic CMO.</td>
</tr>
<tr>
<td>Flach 1987</td>
<td>Randomised double masked, crossover study.</td>
<td>Number randomised: 24, 22 followed up to 2 months.</td>
<td>Topical 0.5% ketorolac tromethamine v placebo four times daily for 4 weeks.</td>
<td>Aphakic and pseudophakic eyes with acute CMO.</td>
</tr>
<tr>
<td>Heier 1983</td>
<td>Randomised double masked.</td>
<td>Number randomised: 28, 26 completed the study.</td>
<td>One drop topical 0.5% ketorolac tromethamine and artificial tears v prednisolone acetate and one drop topical 0.5% ketorolac tromethamine and artificial tears v prednisolone acetate and combination four times daily for a maximum of 12 weeks. Treatment tapered earlier if CMO resolved.</td>
<td>Aphakic and pseudophakic eyes with acute CMO.</td>
</tr>
<tr>
<td>Rho 1991</td>
<td>Randomised un-masked.</td>
<td>Number randomised: 34</td>
<td>Topical 0.5% ketorolac tromethamine v topical 0.1% diclofenac sodium one drop four times daily.</td>
<td>Pseudophakic eyes with acute CMO.</td>
</tr>
</tbody>
</table>

Figure 1 Improvement of vision at end of treatment.

RR (fixed) 95% CI

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>NSAID n/N</th>
<th>n/N</th>
<th>RR (fixed) 95% CI</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yannuzzi 1977</td>
<td>1/10</td>
<td>3/10</td>
<td>18.46 (0.04, 2.69)</td>
<td></td>
</tr>
<tr>
<td>Burnett 1983</td>
<td>3/6</td>
<td>3/8</td>
<td>15.82 (0.40, 4.43)</td>
<td></td>
</tr>
<tr>
<td>Flach 1987</td>
<td>8/13</td>
<td>1/13</td>
<td>6.15 (1.16, 5.520)</td>
<td></td>
</tr>
<tr>
<td>Flach 1991</td>
<td>22/46</td>
<td>10/49</td>
<td>59.37 (1.25, 4.40)</td>
<td></td>
</tr>
</tbody>
</table>

Favours placebo  Favours NSAID

0.1 0.2 0.5 1 2 3 5 10

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### Comparison: NSAID versus placebo in chronic CMO

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>NSAID</th>
<th>Placebo</th>
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<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
</tr>
<tr>
<td>Yannuzzi 1977</td>
<td>2/10</td>
<td>4/10</td>
</tr>
<tr>
<td>Flach 1987</td>
<td>5/13</td>
<td>2/13</td>
</tr>
<tr>
<td>Flach 1991</td>
<td>21/41</td>
<td>7/46</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>RR (fixed)</th>
<th>Weight %</th>
<th>RR (fixed)</th>
</tr>
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<tr>
<td></td>
<td>31.75</td>
<td>0.50</td>
<td>(1.21, 2.14)</td>
</tr>
<tr>
<td></td>
<td>15.88</td>
<td>2.50</td>
<td>(0.59, 10.64)</td>
</tr>
<tr>
<td></td>
<td>52.37</td>
<td>3.37</td>
<td>(1.60, 7.09)</td>
</tr>
</tbody>
</table>

**Figure 2** Improvement of vision 1 month after treatment.

- Though all three trials used 0.5% topical ketorolac tromethamine as the NSAID, the NSAID was compared with different interventions.
- The duration of treatment varied in all three trials.
- The duration of CMO was less than 45 days in one study,\(^7\) 45–49 days in the study by Heier et al.,\(^6\) and 60–90 days in Flach’s trial.\(^3\)
- The cataract surgery was different in the three trials.\(^5–7\) The duration of CMO was less than 45 days in one study,\(^7\) 45–49 days in the study by Heier et al.,\(^6\) and 60–90 days in Flach’s trial.\(^3\)
- The variability in results can also be explained by the fact that different NSAIDs were used in the various trials. Oral indomethacin was found to be ineffective in the treatment of clinical chronic CMO. Topical fenoprofen was not shown to be effective. The only NSAID found to be effective is topical 0.5% ketorolac tromethamine.\(^6–10\)

**CONCLUSION**

The evidence of the effectiveness of NSAIDs for acute or chronic CMO is insufficient to clearly inform practice. The therapeutic effect of NSAIDs on CMO needs to be assessed by larger trials with longer follow up.

### ACKNOWLEDGEMENTS

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### REFERENCES

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