**Topical nonsteroidal anti-inflammatory drugs in the prevention of pseudophakic cystoid macular edema following phacoemulsification: A systematic review**

Ni Putu Ayu Pande Dewi¹, Cokorda Istri Dewiyani Pemayun²

**ABSTRACT**

**Introduction:** The goal of surgeons to avoid Pseudophakic Cystoid Macular Edema (PCMO) has led to the widespread use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) after cataract surgery, although current research into the best anti-inflammatory drugs to avoid PCMO is still underway. This review aimed to determine the efficacy of topical NSAIDs in preventing PCMO following phacoemulsification.

**Methods:** This systematic review was built on the recommended reporting items for systematic reviews and meta-analyses (PRISMA) and PICO criteria for papers during the previous 10 years. The keywords was searched by Boolean operator: “NSAIDs” AND “Prevention” AND “Cystoid Macular Edema” AND “Optical Coherence Tomography” AND “Phacoemulsification”. According to STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist, the quality of each chosen article was evaluated.

**Results:** We have selected five articles of prospective cohort studies, which involved 756 patients whom received topical NSAIDs (Naprafenac 0.3%, Ketorolac Tromethamine 0.4%, Nepafenac 0.1%, and Diclofenac 0.1%) in treatment group and 700 patients received Placebo (Artificial tears) in control group. There was significant difference of central macular thickness based on OCT results between NSAIDs and control (placebo) group after uneventful phacoemulsification. Additionally, NSAIDs used as a preventative before phacoemulsification procedure exhibited a significantly reduced rise in central foveal thickness compared to placebo. There were changes of central macular thickness postoperatively, and were significantly different from preoperative.

**Conclusion:** It has been demonstrated that topical NSAIDs successfully lower the incidence of Pseudophakic Cystoid Macular Edema following phacoemulsification.

**Keywords:** NSAIDs, Cystoid Macular Edema, Phacoemulsification.


**INTRODUCTION**

Cataract is a disease in which the lens of the eye becomes opacified and could block the passage of light. It is a gradual and progressive clouding and thickening of the lens that could cause severe visual impairment and blindness worldwide. Even though it is treatable, this illness continues to rank among the most widespread health issues in underdeveloped nations. According to studies, there are 36 million blind persons in the world, and cataracts are to blame for more than 12 million of those cases.¹ ² The onset of cataracts is progressive and gradual with aging, therefore the incidence is common in older age. Americans older than 40 years, approximately 20.5 million (17.2%) had cataracts in either eye and these numbers are estimated to be 30.1 million, while the cases of pseudophakia/aphakia reach 9.5 million.¹ ³

In line with the sharp increase in cataract patients, there have been an increasing number of cataract procedures. The number of complications following cataract surgeries has been rising as a result of mechanical damage, an adverse reaction to the implanted intraocular lens, and various inflammations that may occur, despite the fact that remarkable advancements in cataract surgery, such as phacoemulsification with ultrasonography, have been made.¹ ⁴ ⁵ ⁶ Surgical trauma causes the release of prostaglandin that could increase the permeability and dilatation of vascular. Pseudophakic Cystoid Macular Edema (PCMO), one of the most common complications following cataract surgery, could result from this. It is characterized by the accumulation of fluid in the macular region, particularly in the outer and inner nuclear layers. The exact pathogenesis remains unclear and multifactorial, but inflammation takes a major role in the pathogenesis of PCMO. Surgical manipulation following phacoemulsification within the anterior chamber causes the arachidonic acid released by uveal tissue and leads to the production of Prostaglandin (PGs).
via cyclooxygenase (COX) pathway or Leukotrienes via the Lipooxygenase pathway. It diffuses posteriorly to the vitreous and causes disruption of blood-retinal barriers thus leading to swelling of the fovea due to the increase of vascular permeability and accumulation of fluid.6,9

The incidence of PCMO between 0.2–2% varies depending on how PCMO is determined by Fluorescein Angiography (FA), Optical Coherence Tomography (OCT), or by clinical examination alone. The accurate way to measure macular thickness is using OCT; besides it also can use to determine whether macular edema is present, and determine the long-term effects of different treatments.10–12 Phacoemulsification technology and incision technique have developed and the incidence decreased to 0.2–2.5% but the PCMO is still one of the most complications following uneventful phacoemulsification which causes unfavorable visual impairment.10,11,13 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) through their mechanism of action inhibit Cyclooxygenase (COX) enzyme and thereby inhibit the synthesis of prostaglandin, which is thought to be the primary pathogenesis in macular edema; however, they could become one of the beneficial agents to prevent PCMO and speed up visual recovery after cataract surgery. Therefore, the prevention of PCMO is very important and still being debated in many studies.5 Nepafenac, bromfenac, ketorolac, diclofenac, and flurbiprofen have all received FDA approval for use as topical NSAIDs in PCMO.7 Topical NSAIDs are preferred over steroids as PCMO preventive medications after cataract surgery, according to research by Kessel et al.14 The benefits of NSAIDs include analgesia, decreased risk of subsequent infection, and IOP stability. The goal of the surgeons to avoid PCMO has led to the widespread use of NSAIDs after cataract surgery, although current research into the best anti-inflammatory drugs to avoid PCMO is still underway.10

The purpose of this systematic review is to review the role of NSAIDs in the prevention of Pseudophakic Macular Edema after phacoemulsification.

METHODS

Literature Search and Selection

To enhance transparency, the literature search was carried out using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The study question and inclusion criteria were addressed using the PICO criteria:

- **Population (P)**: patient after uneventful phacoemulsification,
- **Intervention (I)**: whom received topical NSAIDs compared to placebo (artificial tears),
- **Comparison (C)**: are there significant differences of central subfield thickness between NSAIDs group and control group based on OCT results following phacoemulsification,
- **Outcome (O)**: results following phacoemulsification.

Targeted articles were within 10 years of publication which were extracted based on the countries in which the study was conducted, methods (study design, settings, sample size, period of study, participants demographics). Selected articles must be in English and specifically on NSAIDs and the desired outcomes. The strength of each publication was then assessed using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist.

Pubmed and Google Scholar were used as database. We identified with keywords relevant to the topic using the Boolean operator to be specific on the topics. Keywords used: "NSAIDs" AND "Prevention" AND "Cystoid Macular Edema" AND "Optical Coherence Tomography" AND "Phacoemulsification".

From the selected articles, we extracted results, discussion and other essential components of the article to determine its overall quality. Finally careful review of all sections was done to complete the systematic review procedure.

Data Collection

From the selected articles, we extracted some key points to collect data needed for this systematic review such as the main author, year of publication, study design, total number of participants involved, types, dosage, and outcome of the treatment of each study. Quantitative data of each outcome are the results of Pseudophakic Cystoid Macular edema after phacoemulsification.

RESULTS

Literature Selection

All selected articles were published in the last ten years. We have selected five articles of prospective cohort studies. The five studies involved 756 patients who received topical NSAIDs (Nepafenac 0.3%, Nepafenac 0.1%, Ketorolac Tromethamine 0.4%, and Diclofenac 0.1%) in the treatment group and 700 patients received Placebo (Artificial tears) in the control group. It was shown that the central macular thickness based on OCT was significantly different between NSAIDs and the control (placebo) group after uneventful phacoemulsification. Therefore, following uneventful phacoemulsification, topical NSAIDs effectively decreased the incidence of pseudophakic cystoid macular edema. Prostaglandin was released during phacoemulsification, which could enhance vascular permeability and dilation, leading to central macular edema.

By reducing prostaglandin synthesis through their mode of action, which targets Cyclooxygenase 1 and 2 (COX-1 and COX-2) enzymes, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) can lessen the possibility of central macular edema after phacoemulsification.

Among five journals reviewed, one journal showed no significant difference in central macular thickness based on OCT results between the NSAIDs and placebo.
groups. Interestingly, this was found in a study by the same researcher in a different year by excluding risk factors for macular edema or conditions that exacerbate macular edema. It is possible because the sample difference in the two studies was >50% and the different concentrations of NSAIDs (nepafenac 0.3% vs 0.1%) used in the studies.

**Risk of Bias**

Based on the STROBE checklist, all five articles had fulfilled the criteria, thus well written.

**DISCUSSION**

One of the most frequent side effects of phacoemulsification is pseudophakic cystoid macular edema (PCME), which in certain circumstances can cause permanent vision loss. Cyclooxygenase (COX) enzymes are chemically inhibited by nonsteroidal anti-inflammatory drugs (NSAIDs), which prevent the formation of prostaglandins. NSAIDs seem to be beneficial in preventing cystoid macular edema following phacoemulsification through their mechanism to inhibit prostaglandin that takes roles in pathogenesis in CME. Different NSAIDs types, including bromfenac, nepafenac, diclofenac, flurbiprofen, and ketorolac tromethamine, have been suggested for the prevention of PCME. Nepafenac has received approval in Europe to treat inflammation following cataract surgery and to lessen retinal edema. Nepafenac is a medication that comes in two different forms: nepafenac 0.1% three times per day, and nepafenac 0.3% once daily. OCT is a reliable method for identifying CME since it can indicate foveal cysts, early-stage morphologic changes, is non-invasive, accurately measures macular thickness, detects macular edema, and provides access to the advantages of different treatments over time. Nepafenac 0.3%, administered once daily, was shown to have a lower central macular thickness than Nepafenac 0.1% which given four times daily, according to Bardoloi et al. However there aren’t enough research, nevertheless, to provide information on long-term benefits, various NSAID types, concentrations utilized, inclusion criteria, patient characteristics, prescriptions, and the duration of NSAID used for therapy.

This outcome, however, differs with that of a research by Tzelikis et al., which demonstrated that there was no significant difference in central macular thickness between the NSAIDs and placebo groups based on OCT results. Interestingly, it is shown in a study by the same researcher in a different year by excluding risk factors for macular edema or conditions that exacerbate macular edema. It is possible because the sample difference in the two studies was >50% and the NSAIDs (nepafenac 0.3% vs 0.1%) used in the studies were different in concentration. Nepafenac 0.3 %, administered once daily, was shown to have a lower central macular thickness than Nepafenac 0.1% which given four times daily, according to Bardoloi et al. However there aren’t enough research, nevertheless, to provide information on long-term benefits, various NSAID types, concentrations utilized, inclusion criteria, patient characteristics, prescriptions, and the duration of NSAID used for therapy.
Table 1. Details of Included Studies in this Systematic Review

<table>
<thead>
<tr>
<th>First Author (Publication Year)</th>
<th>Study Design</th>
<th>Sample Size (N)</th>
<th>NSAID Group</th>
<th>Dosage</th>
<th>Control Group</th>
<th>Identified Outcome</th>
<th>Results Summary</th>
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</table>
| McCafferty et al. (2017)        | Prospective Cohort    | NSAID: 503       | Nepafenac 0.3% | Once daily and continuing for 5 weeks                                   | Sterile saline drop (once daily for 5 weeks)                                 | OCT                | 1. When compared to a placebo, topical nepafenac 0.3% statistically significant reduced the incidence of PCME (Pseudophakic Cystoid Macular Edema) ($p$=0.0001)  
2. Significant macular volume change after 5 weeks postoperative compared to preoperative ($p$=0.032)  
3. Significant macular volume change after 5 weeks postoperative compared to preoperative in groups with risk factor ($p$=0.003)  
Nepafenac 0.3% compared to placebo had a statistically significant effect on macular volume change in patients with risk factors after 5 weeks of treatment ($p$=0.031). |
| Tzelikis et al. (2018)          | Prospective Cohort    | NSAID: 103       | Nepafenac 0.3% | Starting once daily 2 days before phacoemulsification and continuing for 5 weeks postoperative | Artificial tears (once daily start 2 days before phacoemulsification and continued to 5 weeks postoperative) | OCT                | 1. Between the nepafenac group and the control group, there was a statistically significant difference in central subfield thickness at 5 weeks ($p$=0.01) and 12 weeks ($p$=0.03).  
2. Between the nepafenac group and the control group, there was a statistically significant difference in total macular volume at 5 weeks ($p$=0.001) and 12 weeks ($p$=0.006).  
3. Based on SD-OCT measurements, 36 eyes (32.1%) in the nepafenac group and 53 eyes (47.3%) in the control group had retinal thickness of greater than 10 m ($p$=0.029). |
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<tr>
<td>Alnagdy et al. (2018)</td>
<td>Prospective Cohort</td>
<td>NSAID: 40 Placebo: 40</td>
<td>a. Nepafenac 0.1% b. Ketorolac tromethamine 0.4%</td>
<td>4 times a day start 2 days preoperative and continued 2 months postoperative</td>
<td>Artificial tears (4 times a day start 2 days preoperative and continued 2 months postoperative)</td>
<td>OCT</td>
<td>1. From the first to the third month post-operative, there was a significant difference in Central Macular Thickness (CMT) between the NSAID groups and the control group ($p=0.008$, $0.027$, and $0.004$, respectively).&lt;br&gt;2. From the first to the third month post-operative, there was no significant difference in Central Macular Thickness (CMT) between the Nepafenac group and the ketorolac group ($p=0.9$, $0.52$, $0.8$, respectively).&lt;br&gt;3. Between the NSAIDs groups and the control group, there was a statistically significant difference in the changes in central macular thickness from pre-operative to the third month following surgery ($p=0.001$).</td>
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<tr>
<td>Tzelikis et al. (2014)</td>
<td>Prospective Cohort</td>
<td>NSAID: 86 Placebo: 40</td>
<td>a. Nepafenac 0.1% b. Ketorolac tromethamine (0.4%)</td>
<td>3 times a day of one drop nepafenac 0.1% 2 days preoperative and continued 4 weeks postoperative b. 4 times a day of one drop ketorolac tromethamine 0.4% 2 days preoperative and continued 4 weeks postoperative</td>
<td>Artificial tears (4 times a day start 2 days preoperative and continued 4 weeks postoperative)</td>
<td>OCT</td>
<td>1. NSAIDs (Nepafenac 0.1% group and Ketorolac tromethamine 0.4% group) and the control group did not differ in central foveal thickness at 1, 4, or 12 weeks ($p=0.89$, $p=0.77$, and $p=0.54$, respectively).&lt;br&gt;2. At 1, 4, and 12 weeks, there was no statistically significant difference in total macular volume between the NSAID groups (Nepafenac 0.1% group and Ketorolac tromethamine 0.4% group) and the control group ($p=0.47$, $p=0.43$, and $p=0.37$).</td>
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<tr>
<td>Medic et al. (2017)</td>
<td>Prospective Cohort</td>
<td>NSAID: 24 Placebo: 20</td>
<td>Diclofenac 0.1%</td>
<td>4 times a day 7 days before surgery and continued until 30 days after surgery</td>
<td>Topical dexamethasone 0.1% for 30 days following surgery and placebo (4 times per day starting 7 days before to surgery).</td>
<td>OCT</td>
<td>1. Patients in NSAID group had a significantly smaller increase in central foveal thickness after phacoemulsification compared to patients in control group ($p&lt;0.001$).</td>
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CONCLUSION

Following phacoemulsification, topical nonsteroidal anti-inflammatory drugs (NSAIDs) are useful for preventing pseudophakic macular edema. More research is still needed to determine the ideal NSAID concentration, treatment duration, and long-term outcomes.

AUTHOR CONTRIBUTION

Writing this manuscript involved the participation of all authors.

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CONFLICT OF INTEREST

All authors understood and consented to the publishing of the final paper, and there were no conflicts of interest.

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18. Tzelikis PF, Vieira M, Hida WT, Motta AF, Nakano CT, Nakano EM, et al. Comparison of Ketorolac 0.4% and Nafenac 0.1% for the


