Role of Topical NSAID’s in Post-operative CME

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No financial interest
**Value of NSAID in ocular surgery**

- Prevention and treatment of cystoid macular edema (CME) following cataract surgery\(^1,2\)
- Management of postoperative inflammation\(^3\)
- Prevention of intraoperative miosis during cataract surgery\(^3\)
- Reduction of pain and discomfort following surgery or injury\(^4-7\)


**NSAID Mechanism of Action**

- Prostaglandins are the main causative factor of postoperative inflammation and CME
- NSAIDs inhibit the cyclooxygenase (COX) pathway, limiting prostaglandin formation\(^1\)
- Steroids act by reducing prostaglandin synthesis through inhibition of Phospholipase A\(^2\) and decreasing availability of cellular arachidonic acid\(^4\)
- Combined administration of corticosteroids and NSAIDs shown to provide synergistic action resulting in more rapid resolution of symptomatic CME\(^5,3\)

NSAIDs and CME

- CME is the most common cause of visual decline following uncomplicated cataract surgery (estimated to occur in 12% of low-risk cataract cases).

- CME development is due to prostaglandins release and the break down of blood-retinal barrier.

- Late onset (4 to 6 weeks post-operatively)


Courtesy of University of Pittsburgh Visual Imaging
CME

- **Asymptomatic CME**
  - May not be associated with significant visual loss, but mild fluorescein angiographic or OCT evidence of macular oedema

- **Symptomatic CME**
  - Described as angiographic or OCT evidence of vessel leakage associated with visual acuity of 20/40 or worse


Optical Coherence Tomography (OCT)

- Main diagnostic tool for CME
- Can measure even subtle postoperative retinal thickening
  - Along with contrast sensitivity test

High risk CME Patients

- Uveitic patients with pre-existing ocular inflammation
- Patients with ocular vascular disorders sp. Diabetic patients
- Epi-retinal membranes or vitreo-retinal interface disorders
- Glaucoma patients & Retinitis pigmentosa

Prophylaxis should be started earlier and extended longer for high-risk patients

Hypothesis on Mechanism of CME Formation Following Cataract Surgery

- High levels of PGs in aqueous and vitreous in high risk patients
- Breakdown of the Blood Aqueous Barrier & Blood Retina Barrier
- Accentuated by Operative Irritation/Inflammation

Cystoid Macular Edema

Role of NSAIDs in Prevention of CME??

Achieving adequate intraocular therapeutic concentrations is important to maximize effect of therapy on target tissue - retina.

Steroids alone do not effectively prevent or treat CME.

Preoperative and postoperative topical NSAIDs help in preventing and treating post-surgical CME by reducing intraocular PG levels.

Efficacy Comparison of Topical NSAIDs & Steroids in Reducing Incidence of CME

Patients undergoing cataract surgery (N = 60)

**Group 1: Post-Op NSAID + Corticosteroid**

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<thead>
<tr>
<th>NSAID</th>
<th>Corticosteroid</th>
<th>NSAID + Corticosteroid</th>
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<tbody>
<tr>
<td>-2 Day</td>
<td>-1 Day</td>
<td>Day of Surgery</td>
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<td>Week 1</td>
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**Group 2: Post-Op Corticosteroid alone**

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Efficacy Comparison of Topical NSAIDs & Steroids in Reducing Incidence of CME

Results (evaluation at week 6)¹

- Group 1: 0% CME
- Group 2: 12% CME

NSAID used pre-operatively and post-operatively minimizes the incidence of patient treatment for CME


Cataract NSAID Treatment Regimen¹

Recommended NSAID Dosing

- At-Risk Patients
  - Preoperative: 1 week
  - Postoperative: 4 weeks to several months

- Not At-Risk Patients
  - Preoperative: 1-2 Days
  - Postoperative: 4 weeks

Adverse Events Commonly Associated with Conventional NSAID Therapy

- NSAIDs frequently associated with unpleasant side effects:
  - Burning and irritation
  - Superficial punctate keratitis
  - Delayed wound healing

- Rare but Severe corneal issues also reported with conventional NSAIDs:
  - Corneal thinning, melting or perforation

Review of Common Conventional NSAIDs*

- Diclofenac 0.1% and Ketorolac 0.5% shown to be equally effective in:
  - Treating post-cataract CME
  - Treating post-operative inflammation

- Ketorolac 0.4% indicated for post-refractive pain*

- Newly introduced now is Nepafenac (Nevanac, Alcon)

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3. Prescribing Information: VOLTAREN*, ACULAR*, ACULAR* LS. *Trademarks are the properties of their respective owners.
5. Flach AJ et al. Comparative effect of diclofenac 0.1% and ketorolac 0.5% on inflammation after cataract. Ophthalmology 1998;105:1775-779.

* Comparison based on US package inserts.
Nepafenac Ophthalmic Suspension 0.1% (NEVANAC®)

Advantages over conventional NSAID in treating ocular inflammation and CME:

- Smaller dose to reach therapeutic levels (One drop TID one day pre-op, DOS, 14 days post-op) → minimizes side effects
- Physiologic pH (7.4) → and reduced burning & irritation
- Only Ophthalmic NSAID prodrug → better penetration and less ocular surface side effects and high selectivity in CME.

Prodrug Structure: Metabolic Conversion

- Nepafenac is converted to a potent cyclooxygenase inhibitor, Amfenac, by intraocular hydrolases

**Prodrug**

High permeation and penetration power over cornea and to posterior segment
- Less ocular surface side effects as the drug rapidly penetrates into anterior and posterior segments

Higher selectivity to target cells in retina
- Retina/choroid > iris ciliary body > cornea = minimal systemic absorption (1,700X less single oral dose)

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**Prodrug structure of nepafenac serves as a reservoir for continued amfenac formation**

high intraocular therapeutic levels in small administered doses

Commercial nepafenac 0.1% suspension (amfenac plus nepafenac) demonstrated significantly greater ocular bioavailability of drug than either ketorolac 0.4% or bromfenac 0.09% solutions
Degree of Corneal Permeation of Various NSAIDs

- **Ketorolac**
- **Bromfenac**
- **Diclofenac**
- **Nepafenac**

Covalently bound and uncharged nepafenac molecule increases corneal permeability coefficient and drug distribution within ocular tissue.


Role of NEPAFENAC in Cataract surgery

- **NEVANAC® Suspension** is effective in treatment of anterior segment inflammation and ocular pain after surgery\(^1\)\(^2\)

- **NEVANAC® Suspension** helps in the prevention and treatment of CME specially in high risk patients

Nepafenac maintains its action in prevention and treatment of CME through:

- **Enzymatic effect**
  - Targeting and inhibiting intraocular cyclooxygenase
  - Maintains stability of all ocular blood barriers

- **Arachidonic acid pathway similarity** (by having a metabolic pathway similar to arachidonic acid)
  - Inhibits all prostaglandins of the ICB
  - Inhibits retina PGE₂ synthesis
  - Maintains the integrity of the BRB

In conclusion

- Nepafenac 0.1% gives an enhanced therapeutic potential for a variety of conditions associated with retinal edema as it has superior pharmacodynamic properties in the posterior segment compared to Diclofenac 0.1% and Ketorolac 0.5%.