Better ophthalmic surgery outcomes in recent years have created more Demanding Patients.
NSAIDs can play a pivotal role in facilitating cataract surgeries, getting a better visual outcome with a rapid and safe convalescence.

NSAIDs can optimize the surgical experience for patients undergoing PRK and LASIK.
1. Maintain pupillary dilatation during cataract surgery.
2. Prevention and management of post operative inflammation.
3. Prevention and management of post operative cystoid macular edema.
**1 - Pupillary dilatation**

NSAIDs help to maintain pupillary dilatation during cataract surgery.

**Decrease Intraoperative Miosis**

- Miosis may obstruct surgeon’s view during cataract surgery, thus creating a hindrance to the surgical procedure\(^1\).
- Miosis associated with increased complications and posterior capsular rupture\(^1\).
- When dosed preoperatively, NSAIDs play significant role in decreasing intraoperative miosis\(^2\).

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*Courtesy of University of Pittsburgh Visual Imaging*
II – Prevention and management of post operative inflammation

Cataract NSAID Treatment Regimen

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

- CME is the most frequent cause of visual decline following uncomplicated cataract surgery
- Normally occurs 4 to 6 weeks post-op
- Studies show CME occurs in up to 12% of cases

Definition of CME

- **Angiographic CME**
  - May not be associated with significant visual loss, but fluorescein angiographic evidence of macular edema

- **Clinical CME**
  - Described as *vessel leakage* associated with visual acuity of 20/40 or worse
  - Today’s definition is becoming *stricter* (20/25 or worse) due to higher patient *expectation.*

- Can measure even subtle postoperative retinal thickening
- Gaining popularity for diagnosis of CME
  - Along with contrast sensitivity test


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Optical Coherence Tomography (OCT)

- Can measure even subtle postoperative retinal thickening
- Gaining popularity for diagnosis of CME
  - Along with contrast sensitivity test


Courtesy of University of Pittsburgh Visual Imaging
Risk Factors for CME

- Pre-existing ocular inflammation
- Epi-retinal or vitreo-retinal interface membrane problems
- Diabetic retinopathy
- Patients suffering from ocular vascular or cardiovascular disease
- Patients with history of retinitis pigmentosa
- Prophylaxis should be started earlier and extended longer for high-risk patients\(^1\)


Hypothesis on Mechanism of CME Formation Following Cataract Surgery

Operative Irritation/Inflammation
- Aging
- Systemic Vasculopathy
- Glaucoma

Prostaglandins in Aqueous & Vitreous

Breakdown of the Blood Aqueous Barrier & Blood Retina Barrier

Cystoid Macular Edema

Patients’ expectation have changed. They now expect excellent vision immediately. In the era of multifocal IOLs even a very mild CME will reduce the performance of the lens, thus it is mandatory with these IOLs to avoid CME in the post operative period.
Topical NSAIDs are effective in preventing postsurgical angiographic CME\(^1\)

NSAID therapy also shown to have beneficial effect on visual function\(^1\)

Critical to achieve therapeutic concentrations in posterior chamber to maximize effect of NSAID therapy on target tissue - retina\(^2\)

Steroids alone do not effectively prevent or treat CME\(^3\)

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Proper dosing of NSAIDs maximizes success and minimizes complications.

Proper dosing includes:
- Dosing 4 weeks post-op in cataract patients to prevent CME.
- Limit dosing in a compromised cornea... this includes PRK.
- In PRK, NSAIDs should be dosed 3-4 times a day while the patient experiences pain (2-3 days) and then discontinued.

Avoid NSAIDs in patients with severe dry eye.

Recommended NSAIDs Dosing

**Routine-Risk Patients**
- Preoperative: 4 times daily for 2-3 days.
- Post operative: 4 times daily for 4 weeks.

**Higher-Risk Patients**
- Preoperative: 4 times daily for 1 week.
- Post operative: 4 times daily for 4 weeks to several months.
They are excellent pain control for PRK and PTK patients.

Refractive NSAID Treatment Regimen

- **Recommended NSAID Dosing**
  - **LASIK**
    - Dry stromal bed for 1 minute, Remove speculum, Dose post-operatively
  - **Surface Ablation**
    - Dose after bandage contact lens
    - Dose post-operatively for 2-3 days

- NSAIDs in refractive surgery used primarily for analgesic effect
- Immediate post-op use
- NOT to be dosed for the entire epithelial wound healing process


*Trademark is the property of its owner.*
The Ideal NSAID

- Ability to penetrate target intraocular tissues at therapeutic levels:
  - Aqueous humor: cell/flare reduction
  - Posterior segment: CME prevention
- Excellent anti-inflammatory efficacy
- Excellent analgesic properties
- Safe and comfortable

A Novel Class of Non-Steroidal Anti-Inflammatory Therapy
Indication:
- Treatment of pain and inflammation following cataract surgery

Dosing:
- One drop TID one day pre-op, DOS, 14 days post-op

Formulation:
- First and only ophthalmic non-steroidal prodrug
- Preservative: 0.005% BAK
- pH: 7.4 (physiologic)

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


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Optimizes Activation
- Upon ocular dosing, nepafenac metabolized by intraocular tissues

Target-Specific Efficacy
- Nepafenac is converted into amfenac for optimal efficacy
- Retina/choroid > iris ciliary body > cornea

Minimizes toxicity
- Ocular surface complications associated with conventional NSAID therapies may be minimized
  - Drug rapidly distributes into anterior and posterior segments

- Cornea, anterior and posterior chamber safety demonstrated in vivo via slit-lamp biomicroscopic examination in two long-term pre-clinical studies
  - 3-month study and 6-month study

- Minimal systemic absorption
  - 1,700x less than single oral dose

Degree of Corneal Permeation of Various NSAIDs

- Ketorolac
- Bromfenac
- Diclofenac
- Nepafenac

Corneal Permeability (cm/sec x 10^-5)


Evaluation of Analgesic Effect Following PRK

- **Purpose**
  - Evaluation of safety/efficacy of nepafenac 0.1% ophthalmic suspension vs. diclofenac 0.1%
    - Reduction of pain associated with PRK

- **Methods**
  - 60 patient, multi-center, randomized, double-masked, parallel groups
  - **Dosing:**
    - 2 drops preoperatively, 1 drop one hour after surgery, QID postoperatively for 2 days

Pain Scores following PRK

Severe

None

Day 1 -
am
Day 1 -
noon
Day 1 -
pm
Day 1 -
Bedtime
Day 2 -
am
Day 2 -
noon
Day 2 -
pm
Day 2 -
Bedtime

Nepafenac 0.1%  Diclofenac 0.1%

* p = 0.0305


PRK Epithelial Healing Results

Percentage of Patients with Complete Reepithelization

Day 3  Day 7

Nepafenac 0.1%  Diclofenac 0.1%

Anterior Chamber Efficacy

Inhibition & Treatment of Post-Operative Inflammation

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Results demonstrate the superior pharmacodynamics and longer duration of action of nepafenac 0.1%.

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

Overall, nepafenac 0.1% exhibits superior anti-inflammatory properties vs conventional NSAIDs such as diclofenac 0.1%.

Purpose
- Efficacy evaluation of NEVANAC® Ophthalmic Suspension in decreasing pain and inflammation following cataract surgery

Methods
- Multi-center, vehicle-controlled, randomized, double-masked (n=476)
- Dosing:
  - TID 1 day preoperatively, day of surgery, 14 days postoperatively
- Additional topical or systemic anti-inflammatory medications excluded from protocol

*N* < 0.05

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

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Prevention of Cystoid Macular Edema

Nepafenac – Enzymatic Effect

- Uniform potent inhibition
  - Uniformly targets cyclooxygenase of intraocular tissue
  - Affects all ocular blood barriers

- Arachidonic acid pathway similarity
  - Uniformly inhibits all prostaglandins of the ICB
  - Inhibits retina PGE$_2$ synthesis
  - Inhibits BRB breakdown

**Conclusions**

- Nepafenac 0.1% exhibits superior pharmacodynamic properties in the posterior segment following ocular dosing.
  - Unique therapeutic potential for a variety of conditions associated with retinal edema.
- Diclofenac 0.1% and Ketorolac 0.5% were ineffective in reducing inflammation in the posterior segment.

Safety Results

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Nevanac

- NEVANAC® Suspension has been proven safe and well tolerated throughout ocular tissues with no delays in wound healing compared to placebo in animal models\textsuperscript{1,2,3}

- Ocular safety of Nepafenac has been confirmed in pre-clinical studies\textsuperscript{1,2,3}:
  - Concentrations up to 1.5\% (15x commercial concentration)
  - Dosing regimens up to 2 drops QID
  - Treatment duration up to 6 months

- 11 completed clinical studies to date
  - n = 891 across all Nepafenac patients

- Low incidence of adverse events
  - Occurred at rate similar to vehicle
  - No burning or stinging reported in phase III trials\textsuperscript{4,5}

THANK YOU 😊