Perioperative Topical NSAIDs Should Be Used in Routine Cataract Surgery

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Perioperative Topical NSAIDs Perioperative Topical NSAIDs
Should Be Used in Routine Cataract Surgery

Incidence of CME

- The incidence of "clinical" CME is estimated to be between 1% to 12%
- "Subclinical" or angiographic CME can be as high as 39%
  - Macular effects following phacoemulsification should be recognized as CME even without apparent clinical symptoms


Risk Factors for CME

- Preexisting ocular inflammation
- Epiretinal or vitreoretinal interface membrane problems
- Loss of vitreous
- Ocular vascular disease
- Diabetic retinopathy
- Cardiovascular disease
- Hypertension
- History of retinitis pigmentosa
- Posterior segment inflammation
- CME in 1st eye
- Stretching the iris
- TASS

Some Patients Without Risk Factors Develop CME

- CME can develop after surgeries with no obvious complications or in patients without apparent risk factors
- Aging population with cataracts often have hidden risk factors

Why Prevent CME

- More demanding patients
  - Incidence of CME negatively affects your practice
- CME easier to prevent than treat
  - Some cases resolve without treatment
    - Can take months to years
  - Some cases recalcitrant even to aggressive treatment
- Prevention is cost effective
- Resolved CME often leaves impaired function

Pharmacoeconomic Impact of CME

- Significantly higher cost of ophthalmic care among Medicare patients receiving cataract surgery between 1997 and 2001 who developed CME within 1 year of surgery (p < .0001 compared to Non-CME)
How to Prevent CME and Other Negative Effects of Prostaglandin Release

NSAID Mechanism of Action

• NSAIDs inhibit the cyclooxygenase (COX) pathway, thus limiting prostaglandin formation.

• Cyclooxygenase is an enzyme responsible primarily for formation of prostaglandins.
  – COX-1 is more prevalent and is always present throughout the ocular tissues, and therefore it is already present at the time of the surgical injury.
  – COX-2 enzyme is less prevalent, and is inducible by inflammation.

• Prostaglandin formation is a major causative factor of postoperative inflammation and CME.


Arachidonic Acid Cascade: Sites of Steroids and NSAIDs Actions

Using and Choosing NSAIDs for Ocular Surgery

Clinical Benefits of NSAIDs

- Analgesia
- Prevention of intraoperative miosis; maintenance of mydriasis
- Anti-inflammatory activity
- Prevention and treatment of CME
  - Improved visual outcomes

Analgesia

- Most ocular surgery patients experience some pain/discomfort either during or after procedure
  - Less pain = happier patient
- NSAIDs very effective at controlling and preventing pain
  - Analgesic effects enhanced if given preoperatively to allow pre-trauma suppression of prostaglandin synthesis
### Importance of Preventing Miosis/Maintaining Mydriasis

- Sufficient mydriasis allows surgeon access to diseased lens/easier insertion of new lens
- Decrease in pupil diameter increases risks
  - Surgical trauma
  - Postoperative inflammation
  - Posterior capsule rupture

### Ketorolac 0.4% Decreased Patient Discomfort During and After Cataract Surgery

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Intra-operative</th>
<th>Post-operative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo 1 Hour</td>
<td>3.1</td>
<td>2.5</td>
</tr>
<tr>
<td>Placebo 1 Day</td>
<td>1.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Placebo 3 Days</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Intra-operative</td>
<td>0.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Post-operative</td>
<td>0.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*P<0.001 vs 3 days for intra-operative and post-operative
**P<0.001 vs control for intra-operative and post-operative
†P=0.017 vs control for intra-operative day

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### Ketorolac 0.4% Administered 3 Days Before Surgery Maintained Pupil Size at pre-operative diameter

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean Pupil Size (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-operation</td>
<td>7.7</td>
</tr>
<tr>
<td>IOL insertion</td>
<td>7.8</td>
</tr>
</tbody>
</table>

*P < 0.001

N = 100
Preventing CME, Retinal Thickening

CME Prevention Study

Randomized, investigator-masked, multicenter, clinical trial (N=546)

Group 1: Ketorolac 0.4% (preoperatively and postoperatively) plus steroid (postoperatively)

Group 2: Steroid only (postoperatively)

Outcome Measures:
• Comparison of OCT changes
• Final visual acuity
• Contrast sensitivity
• Adverse events


Incidence of CME Based on OCT Image Examination

Percentage of Patients

Definite/Probable Possible Classification Based on OCT Review

Ketorolac/steroid (n = 268) Steroid only (n = 278)

Changes in Retinal Thickness at Week 4

Relation of Retinal Thickness to Visual Acuity and Contrast Sensitivity

Visual Acuity (VA) Slightly Worse in Patients With Retinal Thickening: All Patients
Limiting Retinal Thickening Improves Contrast Sensitivity

Note: includes data from one site only, n = 60.

Mean Contrast Sensitivity at Week 4

Spatial Frequencies (Cycles per Degree)


Implications of Retinal Thickening

- The results from the Wittpenn study corroborate findings presented by Roberts et al at ASCRS 2005.
  - After 4 weeks, patients who didn’t use ketorolac showed a statistically significant increase in macular thickness compared to baseline ($P \leq 0.009$).
- There was an association between even small amounts of retinal thickening (>10 μm) and reduced contrast sensitivity after phacoemulsification, even in this population of low-risk, healthy patients.


Improved Visual Outcomes
**Peri-operative Ketorolac 0.4% for Reducing Postoperative Visual Alterations**

- Prospective, randomized, case control study
- 120 eyes of 120 patients undergoing uncomplicated clear corneal phacoemulsification
  - Grade 2 nucleus sclerosis
  - Normal central foveal thickness (CFT) preoperatively (by OCT)
- Treatment groups
  - Ketorolac: Ketorolac 0.4% QID, 1 day before surgery and 6 weeks after surgery along with postoperative steroids
  - Placebo: Placebo 1 day before surgery and 6 weeks after surgery along with postoperative steroids
- Outcome evaluation at weeks 1, 3, and 8
  - Visual acuity (best-corrected visual acuity [BCVA]; Snellen acuity)
  - Contrast sensitivity (Pelli Robson Chart)
  - CFT (by OCT)

Mathen and Nair. ASCRS.2008

**Ketorolac 0.4% Prevented Reduction in Contrast Sensitivity**

- Week 8 Results
  - Mean visual acuity was similar in both treatment groups
  - 28 (47%) patients treated with placebo plus steroid had reduced contrast sensitivity compared to 0 patients treated with ketorolac plus steroid
  - Ketorolac treatment significantly reduced the mean increases in postoperative CFT compared to placebo (5.3 ± 6.5 µm vs 11.3 ± 8.5 µm; t = 4.255)
- Conclusions
  - Snellen acuity is not a sensitive measure of mild macular edema
  - Routine use of topical NSAIDs benefits every patient by improving contrast sensitivity and reducing changes in CFT

Mathen and Nair. ASCRS.2008

**Longer Preoperative Ketorolac 0.4% Improved Visual Acuity in Immediate Postoperative Period**

- Pretreatment with Ketorolac 0.4% for 1 or 3 days provided significantly better visual outcomes in the immediate post-operative period
- Although there were no significant differences by 3 months, the control group still had poorer mean visual acuity than any other group

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

Patients undergoing cataract surgery (N = 60)

- Group 1: Post Op NSAID + Corticosteroid
- Group 2: Post Op Corticosteroid alone

Results (evaluation at week 6)¹

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


Incidence of Visually Significant Pseudophakic Macular Edema after Uneventful Phacoemulsification in Patients Treated with Nepafenac

Eric Wolf, Alexandra Braunstein, Carolyn Shih, Richard Braunstein
**Purpose**

- To compare the incidence of visually significant macular edema after uneventful phacoemulsification in patients with distinct CME prophylaxis regimens
  - Prednisolone alone vs. prednisolone + nepafenac

**Methods**

- Retrospective chart review of 450 consecutive patients
  - 240 patients treated with prednisolone
  - 210 patients treated with prednisolone + nepafenac
- Baseline characteristics and surgical manipulations were similar between groups

**Prevention of Pseudophakic Macular Edema with Prophylactic Nepafenac 0.1% Suspension**

<table>
<thead>
<tr>
<th>Pre op regimen</th>
<th>N = 240</th>
<th>N = 210</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic</td>
<td>Moxifloxacin 0.5% solution</td>
<td>Moxifloxacin 0.5% solution</td>
</tr>
<tr>
<td>Steroid</td>
<td>Prednisolone acetate 0.1% suspension</td>
<td>Prednisolone acetate 0.1% suspension</td>
</tr>
<tr>
<td>NSAID</td>
<td>None</td>
<td>Nepafenac 0.1% suspension</td>
</tr>
</tbody>
</table>

Patients who developed CME:
- 1 / 240 = 0.42% for prednisolone alone
- 0 / 210 = 0% for prednisolone + nepafenac

Patients treated with nepafenac + prednisolone had a statistically significant lower rate of CME than patients with prednisolone alone.

**Adverse Events Commonly Associated with Conventional NSAID Therapy**

- NSAIDs frequently associated with unwelcome corneal effects:
  - Burning and irritation
  - Superficial punctate keratitis
  - Delayed wound healing
- Severe corneal issues also reported with all conventional NSAIDs:
  - Thinning
  - Perforation due to melts

3. Prescribing Information: Voltaren*; Aculair*; Aculair* LS. *Trademarks are the properties of their respective owners.
Safety and Biocompatibility

- Complications rare
- Most in patients with severe ocular surface disease
- Early cluster of melts largely occurred with generic diclofenac (Falcon)

Conclusions

Evidence for Pre-Cataract and Post-Cataract Duration of Therapy

- Several studies show benefit of pre-operative dosing of NSAIDs
  - 3-day or 1-day significantly improved pupil size and reduced the incidence of CME compared with 1 hour or no pre-operative NSAID
  - 3-day significantly reduced post-operative inflammation compared to patients who received NSAID only after surgery
- Combination of 3 days pre-operative combined with 4 weeks post-operative significantly reduced CME in low-risk patients
- Treating high-risk patients (diabetes, capsule tear, vitreous loss) with NSAIDs for 3 months postoperatively decreased the incidence of CME to that of patients with low CME risk
Personal Guidelines for NSAID Therapy in Cataract Surgery Patients

Recommended NSAID Dosing

At-Risk Patients:
- Pre-operative: 1 week qid (with pred acetate)
- Post-operative: 6-12 weeks qid then taper

Patients not at-risk:
- Pre-operative: 3 days qid
- Post-operative: 1 week qid, then tapering bidx2 wks, qdx3 wks

Prednisolone acetate 1% used post-op on same schedule as NSAIDs unless unmanageable IOP elevation

Conclusion: NSAID Use Should Be Routine

- To avoid poor cataract outcomes
  - CME risk factors very common in cataract surgery population
  - CME prevents full visual recovery after cataract surgery
- To alleviate inflammation and pain
- To limit miosis