CMO/CME
in the Phaco era Myth or Reality?

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Disclosures Sponsorships/Consultant
This is an Alcon sponsored promotional event.
ALCON
Novartis
Zeiss
Allergan
Post Cataract Macular Edema in Diabetic Patients

Objectives

- Understand the development and impact of macular oedema – Irvine-Gass Syndrome Post Cataract Surgery
- Explore the increase in cost of cataract care if patients develop CME
- Explore the increased risk for macular edema development in diabetic patients
- Look at New developments in Post op Cataract Care
### Postoperative Complications Associated With Modern Cataract Surgery

<table>
<thead>
<tr>
<th>Complication</th>
<th>Range of Estimated Incidences (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intraoperative</strong></td>
<td></td>
</tr>
<tr>
<td>Posterior capsular or zonular rupture</td>
<td>1.5 – 3.5</td>
</tr>
<tr>
<td>Vitreous loss/anterior vitrectomy or aspiration</td>
<td>0.8 – 1.39</td>
</tr>
<tr>
<td>Iris/ciliary body injury</td>
<td>0 – 1.2</td>
</tr>
<tr>
<td>Loss of nuclear material into vitreous</td>
<td>0.1 – 0.28</td>
</tr>
<tr>
<td>Suprachoroidal hemorrhage</td>
<td>0 – 0.14</td>
</tr>
<tr>
<td>Retrobulbar hemorrhage</td>
<td>0 – 0.1</td>
</tr>
<tr>
<td><strong>Postoperative</strong></td>
<td></td>
</tr>
<tr>
<td>Cystoid macular edema</td>
<td>1.2 – 3.5</td>
</tr>
<tr>
<td>Corneal edema</td>
<td>0.03 – 5.18</td>
</tr>
<tr>
<td>IOL dislocation, removal, or exchange</td>
<td>0.19 – 1.1</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>0.03</td>
</tr>
<tr>
<td>Retinal tear, break, or detachment</td>
<td>0.14 – 0.9</td>
</tr>
<tr>
<td>Persistent iritis</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Related to inflammation

Note: NEVANAC is indicated in adults for the reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients.

Abbreviation: IOL, Intraocular lens
69 Year old GP Female 8 weeks post uncomplicated Phaco Surgery
Pre op Vision 6/24
Post op 3 weeks 6/6
8 Weeks post op 6/24
Surgery Causes Tissue Damage That Induces Inflammation

Normal Damage from Uncomplicated Surgery

Surgical Complications
- Trauma to Iris
- Eg Iris Hooks
- Prolonged Surgery

Posterior Capsular Tears
Anterior Vitrectomy
Lens fragments

POSTOPERATIVE INFLAMMATION
Inflammation May Lead to Macular Edema by Relaxing the Ocular-Blood Barriers

1. Prostaglandins
2. Prostaglandins
3. Blood-aqueous barrier OPENS
4. Cytokines + Other mediators
5. Diffusion through vitreous to retina
6. Blood-retinal barrier OPENS
7. Fluid accumulates in macula

Macular edema is a painless disorder that affects the central retina, or macula.

Macular edema is caused by the breakdown of the blood-retina barrier, which increases vascular leakage.

Increased vascular leakage causes fluid to accumulate in the macula, which leads to edema and increased macular thickness.

Difficult to differentiate vs DIABETIC MACULAR OEDEMA. Post op Hyperfluorescence of Optic disc on Fundus fluorescein angiography. Treat DME Prior to surgery. On table Anti-VEGF/Steroids

Note: NEVANAC is indicated in adults for the reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients.
Irvine – Gass Syndrome

- Irvine described 1st 1953
- Gass Norton FFA 1966
- Irvine 1976 Survey of Ophthalmology review
- Over 100 Papers on the subject
- Medicare Estimate 47% increase in cost of cataract care if patients develops CME.

Irvine AR A newly defined vitreous syndrome following cataract surgery, interpreted according to recent concepts of the structure of the vitreous. AM J Ophthalol 1953 36: 599-619
Gass JD nortwon EW Cystoid macular edema and papilledema following cataract extraction: a fluorescein fundusscopic and angiographic study. Arch ophthalmol 1966; 76:646-681

2012 Reviews Conceicao Lobo Pseudophakic CME in OphthalmologicaYoshihiro in www.co-ophthalmology.com
Healthy Vs Macular Oedema Retina Fundus Photograph and SD-OCT

?Baseline OCT
Irvine-Gass Syndrome

- Angiographic CME – Normal Vision
  - Normal OCT

- Clinically Significant CME
  - Reduced vision, CME on OCT
  - Within 4 months of surgery-Usually 4-6 Weeks

- Late CME > 4 months

- Chronic CME Lasts > 6 Months

- Diabetic macular oedema VS Irvine-Gass – Co-exist
Aetiology and Risk factors

- Type of Cataract surgery
- Light toxicity
- Vitreo macular traction
- Inflammatory mediators
- Use of Adrenaline in BSS
- Intracameral Drugs eg Cefuroxime
- Vitreous loss
- Integrity of capsule
- Hypertension
- Diabetes
Light Toxicity

- Microscope light Xenon/Halogen
  - Unfiltered (Very blue)
  - UV Filter (Natural Tungsten like)
  - Yellow Filter (very yellow)
- Light occluder made no difference in study. Kraff 1976
- UV Absorbing IOLS ?
- Yellow/Blue <500nm Blocking Lenses?
  - 10/11 Reviews No evidence.

Frequency of Macular Edema Development After Cataract Surgery

Estimated Incidence

Clinically Significant Macular Edema
Associated with decreased visual acuity

≤5.8%

Cystoid Macular Edema
Detected by ocular imaging

4%-20%

Macular Edema Is Associated With Reduced Quality of Vision

Quality of Vision

• Cystoid macular edema is a common cause of decreased vision after cataract surgery.

• Cystoid macular edema can develop even if cataract surgery was successful and uncomplicated.

• Patients may experience vision that is reduced in quality without being reduced in acuity.

Cost of Managing Macular Edema Post Cataract Surgery

Preventing macular edema is likely to result in cost savings in both normal and diabetic patients.

47% higher cost

Note: NEVANAC is indicated in adults for the reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients.

Vitreous Prostaglandin Levels Are Higher in Eyes With Proliferative Diabetic Retinopathy

Compared to patients without any diabetic retinopathy, patients with proliferative diabetic retinopathy have:

- Higher vitreous levels of interleukin-6 (5.4x)
- Higher vitreous levels of interleukin-8 (14.2x)
- Higher vitreous levels of PGE$_2$ (1.5x)
- Higher vitreous levels of TNFα (2.2x)
- Higher vitreous levels of VEGF (33.7x)

Abbreviations. PGE2, prostaglandin E2; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor

Higher Incidence of Postoperative Macular Edema With Diabetes

- Among patients filing Medicare claims for cataract surgery.
- Includes mix of cases with and without diabetic retinopathy.

**NOTE:** Based on patients with 1 or more cataract claims from the 1997–2001 Medicare 5% Beneficiary Encrypted Files; patients were analyzed by diagnosis of cystoid macular edema in the same quarter as or within the following 3 quarters after surgery. Schmier JK, et al. 2007. *Retina.*

<table>
<thead>
<tr>
<th>With Diabetes</th>
<th>Without Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P &lt; .0001</strong></td>
<td><strong>3.05%</strong></td>
</tr>
<tr>
<td>n = 706</td>
<td>n = 2014</td>
</tr>
<tr>
<td>N = 23,122</td>
<td>N = 116,637</td>
</tr>
</tbody>
</table>

*Note:* NEVANAC is indicated in adults for the reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients.
Higher Incidence of Postoperative Macular Edema With Diabetic Retinopathy

- All diabetic patients in the study had mild or moderate diabetic retinopathy.

Vascular leakage was detected in 3 times as many patients with diabetes compared to those without.

<table>
<thead>
<tr>
<th></th>
<th>With Diabetes</th>
<th>Without Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>34</td>
<td>35</td>
</tr>
<tr>
<td>n</td>
<td>26</td>
<td>8</td>
</tr>
</tbody>
</table>

Mean macular volume was larger ($P<0.05$) in the diabetic nonproliferative patient group compared to the group without.

<table>
<thead>
<tr>
<th></th>
<th>With Diabetes</th>
<th>Without Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>34</td>
<td>35</td>
</tr>
<tr>
<td>Mean macular volume ($mm^3$)</td>
<td>7.50</td>
<td>7.12</td>
</tr>
</tbody>
</table>

Note: NEVANAC is indicated in adults for the reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients.


BASELINE 6.65 mm$^3$ 6.79 mm$^3$
Diabetic patients with varying severity of diabetic retinopathy.
All patients had normal center point thickness ≤4 weeks.
All phacoemulsification procedures were performed without complication.

Thicker Macular Edema in Patients With Advanced Diabetic Retinopathy

- Diabetic patients with varying severity of diabetic retinopathy.
- All patients had normal center point thickness ≤4 weeks.
- All phacoemulsification procedures were performed without complication.


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a Center point thickness was measured on OCT as retinal thickness at the center point of the fovea.
b Advanced diabetic retinopathy included moderate and severe nonproliferative diabetic retinopathy, and proliferative diabetic retinopathy.

Reasons for Increased Incidence of Macular Edema After Cataract Surgery in Patients With Diabetes

<table>
<thead>
<tr>
<th>Reason</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher levels of prostaglandins and other proinflammatory cytokines in the vitreous</td>
<td><em>Proliferative diabetic retinopathy vs without diabetic retinopathy</em></td>
</tr>
<tr>
<td>Higher incidence of vascular leakage after cataract surgery</td>
<td><em>Mild or moderate diabetic retinopathy vs without diabetes</em></td>
</tr>
<tr>
<td>Larger mean macular volume after cataract surgery</td>
<td><em>Mild or moderate diabetic retinopathy vs without diabetes</em></td>
</tr>
<tr>
<td>Higher incidence of macular edema diagnosis after cataract surgery</td>
<td><em>Diabetes vs without diabetes</em></td>
</tr>
</tbody>
</table>

Cystoid Macular Oedema after Cataract Surgery

Robert Johnston

Cheltenham General Hospital

Publishing in Ophthalmology
On Line Link will be sent
Risk Factors and Incidence of Macular Edema after Cataract Surgery

A Database Study of 81 984 Eyes

Colin J Chu, Robert L Johnston, Charlotte Buscombe, Ahmed B Sallam, Quresh Mohamed, Yit C Yang for the UK pseudophakic macular edema study group

Ophthalmology – in press
• Director of Medisoft Limited.

• The data extraction and open access fees were sponsored by Alcon, but they have had no involvement in the study design, analysis or interpretation.
Importance & Incidence of CMO

- Cataract surgery common operations performed worldwide.
- Pseudophakic macular edema (PME) is the commonest early postoperative complication to limit vision.

What is the incidence of PME and what are the risk factors?

- Largest previous clinical study was 1,659 eyes in the US. (Henderson et al, 2007)
  - It did not analyse patients with Diabetes.

- This study 81,984 eyes, including those in patients with diabetes, using Medisoft EMR
Role of Non-steroidal’s Singh et al
Macular Thickness
Visual Acuity
Nationally Agreed Datasets

Cataract

Glaucoma

Diabetic Eye Disease

AMD

Retinal Detachment

Royal College of Ophthalmologists’ National Cataract Audit
Structured data
Right click to add as diagnosis

### Visual Acuity

<table>
<thead>
<tr>
<th>Refraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH</td>
</tr>
<tr>
<td>SH</td>
</tr>
<tr>
<td>PMH</td>
</tr>
<tr>
<td>RoS</td>
</tr>
</tbody>
</table>

### IOP

<table>
<thead>
<tr>
<th>RIGHT</th>
<th>LEFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N.A.D.</td>
<td>N.A.D.</td>
</tr>
<tr>
<td>Appl.</td>
<td>Appl.</td>
</tr>
<tr>
<td>Air Puff</td>
<td>Air Puff</td>
</tr>
<tr>
<td>Tono</td>
<td>Tono</td>
</tr>
<tr>
<td>Rebound</td>
<td>Rebound</td>
</tr>
</tbody>
</table>

### Lids / Orbit

- Conj / Sclera
- Cornea
- AC / Gonio
- Pupil / Iris
- Lens

### Vitreous

- Post seg
  - Cystoid macular oedema

### Optic disc

<table>
<thead>
<tr>
<th>C/D</th>
<th>C/D</th>
</tr>
</thead>
</table>

### Motility / Fields

### Drawings
UK & Medisoft unique

- Structured diabetic retinopathy assessment
- Pre & post-operatively
- Use Routinely at Hillingdon Now - National DRSS Grading set
Macular thickening
THH – Quick to enter data – Cannot Save/Print/email till Completed all fields
Precise ETDRS grading

Doctor’s outpatient clinic 16/01/2011

**Right**
- **View R**: good
- **Classification**: NSC
  - **Grading outcome value**: R1
  - **International**: moderate NPDR
  - **International**: diabetic macular oedema absent
  - **ETDRS**: mild NPDR
  - **ETDRS**: no clinically significant macular oedema
- **ETDRS Number**: 35

**Left**
- **View R**: good
- **Classification**: NSC
  - **Grading outcome value**: R3
  - **International**: severe NPDR
  - **International**: severe diabetic macular oedema
  - **ETDRS**: severe NPDR
  - **ETDRS**: clinically significant macular oedema
- **ETDRS Number**: 53

**Screening from 16/01/2011**
- **Classification**: NSC
  - **Grading outcome value**: M0

**This assessment**
- **Classification**: NSC
  - **Grading outcome value**: P0

**Retinopathy**
- **No Lesions of DR**
- **No Maculopathy**

**Visual Impairment**
- **Visual impairment predominantly due to diabetic retinopathy**
<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Description</th>
<th>Last Run</th>
<th>Modified Date</th>
<th>Modified By</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AMD</td>
<td></td>
<td>28/11/2013</td>
<td>16:37</td>
<td>GLOSmedisoft</td>
</tr>
<tr>
<td></td>
<td>Cataract</td>
<td></td>
<td>28/11/2014</td>
<td>15:55</td>
<td>GLOSmedisoft</td>
</tr>
<tr>
<td></td>
<td>Data Sources</td>
<td></td>
<td>07/07/2014</td>
<td>12:05</td>
<td>GLOSmedisoft</td>
</tr>
<tr>
<td></td>
<td>Medical Retina</td>
<td></td>
<td>16/10/2014</td>
<td>12:43</td>
<td>GLOSmedisoft</td>
</tr>
</tbody>
</table>

Items in Home
SQL Server Back Office
Cloud Based
Hospital Based
Instant Live Audits

SQL Server Reporting Services
Cataract

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drillthrough</td>
<td>A bar chart graph of the deviation from predicted spherical equivalent refraction following cataract or clear lens surgery. The most recent measure of post-operative refraction within the specified time period is used.</td>
</tr>
<tr>
<td></td>
<td>Deviation from Predicted Spherical Equivalent Refraction</td>
<td>This report shows the incidence of post-cataract surgery Cystoid Macular Oedema by year of surgery. Filters can be applied to limit the analysis to particular patient/eye groups.</td>
</tr>
</tbody>
</table>

Last Run: 28/11/2014 15:55, Modified By: GLOSmedisoft

Microsoft SQL Server
MySQL
Incidence of Post-Cataract Surgery Cystoid Macular Oedema

(Click on a column to drill-down)
**Report Description**

This report shows the incidence of post-cataract surgery cystoid macular oedema, recorded within 3 months, by year of surgery. Filters can be applied to limit to particular patient/eye groups. An excel data export allows even more detailed analysis.

**Report Criteria**

*Click to View Selected Criteria*

**Report Summary Data**

<table>
<thead>
<tr>
<th>Report Year</th>
<th>Total Cataract Operations</th>
<th>Total Cataract Operations Filtered</th>
<th>Eyes with Post Op CMO</th>
<th>Percentage Eyes with Post Op CMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>4223</td>
<td>4215</td>
<td>49</td>
<td>1.2%</td>
</tr>
<tr>
<td>2010</td>
<td>4231</td>
<td>4227</td>
<td>49</td>
<td>1.2%</td>
</tr>
<tr>
<td>2011</td>
<td>3217</td>
<td>3216</td>
<td>58</td>
<td>1.8%</td>
</tr>
<tr>
<td>2012</td>
<td>3546</td>
<td>3541</td>
<td>82</td>
<td>2.3%</td>
</tr>
<tr>
<td>2013</td>
<td>4031</td>
<td>4026</td>
<td>143</td>
<td>3.6%</td>
</tr>
<tr>
<td>2014</td>
<td>4399</td>
<td>4393</td>
<td>109</td>
<td>2.5%</td>
</tr>
<tr>
<td>2015</td>
<td>89</td>
<td>89</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>23736</strong></td>
<td><strong>23707</strong></td>
<td><strong>490</strong></td>
<td><strong>2.1%</strong></td>
</tr>
</tbody>
</table>
Methods

- 8 centres, IG permission, anonymised data extracted & collated
- No prophylactic NSAIDs
- Diabetic retinopathy status
- Specific filtered single risk factors
  - Epiretinal membrane
  - Previous retinal vein occlusion
  - Previous RD surgery
  - Uveitis
  - PC tear / vitreous loss
  - Prostaglandin analogue use
  - Dry AMD
Group 1

No Diabetes

No risk factors
The incidence of post-operative clinically significant PME of 1.17%

(415 eyes had CMO of 35,563 eyes at risk)
Table 1. Nominal Data Characteristics of the Baseline Reference Cohort (Group 1) Comparing Eyes with Pseudophakic Macular Edema after Surgery with Those without Pseudophakic Macular Edema

<table>
<thead>
<tr>
<th></th>
<th>No Pseudophakic Macular Edema (No. of Eyes)</th>
<th>Pseudophakic Macular Edema (No. of Eyes)</th>
<th>Incidence (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13,679</td>
<td>193</td>
<td>1.391</td>
<td>0.0019</td>
</tr>
<tr>
<td>Female</td>
<td>21,469</td>
<td>222</td>
<td>1.023</td>
<td></td>
</tr>
<tr>
<td>Eye</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>17,377</td>
<td>210</td>
<td>1.194</td>
<td>0.637</td>
</tr>
<tr>
<td>Right</td>
<td>17,770</td>
<td>205</td>
<td>1.140</td>
<td></td>
</tr>
<tr>
<td>Pupil size</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>737</td>
<td>11</td>
<td>1.471</td>
<td>0.538</td>
</tr>
<tr>
<td>Large</td>
<td>29,408</td>
<td>344</td>
<td>1.156</td>
<td></td>
</tr>
<tr>
<td>Surgeon experience</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Junior surgeon (resident)</td>
<td>2459</td>
<td>33</td>
<td>1.265</td>
<td>0.514</td>
</tr>
<tr>
<td>Senior surgeon (consultant)</td>
<td>17,792</td>
<td>197</td>
<td>1.107</td>
<td></td>
</tr>
</tbody>
</table>

Male gender was associated with an increased incidence of postoperative pseudophakic macular edema. Small pupils or surgeons in the early years of training did not show a higher risk of postoperative pseudophakic macular edema. *P* values are shown for chi-square tests with Yates’ correction.
Table 2. Continuous Data Characteristics of the Baseline Reference Cohort (Group 1) Comparing Eyes with Pseudophakic Macular Edema after Surgery with Those without Pseudophakic Macular Edema

<table>
<thead>
<tr>
<th></th>
<th>No Pseudophakic Macular Edema</th>
<th>Pseudophakic Macular Edema</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Standard Deviation</td>
<td>No. of Eyes</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>74.42</td>
<td>10.42</td>
<td>35,146</td>
</tr>
<tr>
<td>Preoperative VA (logMAR)</td>
<td>0.590</td>
<td>0.495</td>
<td>35,109</td>
</tr>
<tr>
<td>Postoperative VA (logMAR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 4 wks</td>
<td>0.224</td>
<td>0.285</td>
<td>15,251</td>
</tr>
<tr>
<td>4–12 wks</td>
<td>0.140</td>
<td>0.243</td>
<td>18,738</td>
</tr>
<tr>
<td>12–24 wks</td>
<td>0.178</td>
<td>0.252</td>
<td>9259</td>
</tr>
<tr>
<td>Axial length (mm)</td>
<td>23.40</td>
<td>1.183</td>
<td>35,137</td>
</tr>
<tr>
<td>IOP (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before surgery</td>
<td>16.15</td>
<td>3.175</td>
<td>26,780</td>
</tr>
<tr>
<td>First within 3 months</td>
<td>14.90</td>
<td>3.374</td>
<td>21,479</td>
</tr>
</tbody>
</table>

IOP = intraocular pressure; logMAR = logarithm of the minimum angle of resolution; VA = visual acuity.

Statistically significant findings included older age in the cystoid macular edema group, with a relatively lower VA at all time points studied. Intraocular pressure decreased after surgery as expected, but was higher in the pseudophakic macular edema group. P values were generated by multiple t tests using the Holm-Sidak method for multiple comparisons using an α of 5.00.
Group 2

No Diabetes

Eyes with a single ‘risk factor’
Group 2 – Eyes with a single ‘risk factor’

<table>
<thead>
<tr>
<th></th>
<th>No PME (eyes)</th>
<th>PME (eyes)</th>
<th>Incidence (%)</th>
<th>Relative risk (and 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epiretinal membrane</td>
<td>229</td>
<td>16</td>
<td>6.53</td>
<td>5.596 (3.452 to 9.074)</td>
</tr>
<tr>
<td>Retinal vein occlusion</td>
<td>218</td>
<td>12</td>
<td>5.22</td>
<td>4.471 (2.556 to 7.820)</td>
</tr>
<tr>
<td>Previous RD repair</td>
<td>479</td>
<td>23</td>
<td>4.58</td>
<td>3.926 (2.604 to 5.919)</td>
</tr>
<tr>
<td>Uveitis</td>
<td>259</td>
<td>9</td>
<td>3.36</td>
<td>2.878 (1.503 to 5.509)</td>
</tr>
<tr>
<td>PC-tear/vitreous loss</td>
<td>477</td>
<td>15</td>
<td>3.05</td>
<td>2.610 (1.573 to 4.339)</td>
</tr>
<tr>
<td>Prostaglandin analogues</td>
<td>3,350</td>
<td>44</td>
<td>1.30</td>
<td>1.111 (0.816 to 1.513)</td>
</tr>
<tr>
<td>High Myopia</td>
<td>3,009</td>
<td>29</td>
<td>0.95</td>
<td>0.818 (0.562 to 1.190)</td>
</tr>
<tr>
<td>Dry ARMD</td>
<td>3,230</td>
<td>30</td>
<td>0.92</td>
<td>0.789 (0.545 to 1.140)</td>
</tr>
<tr>
<td>Reference cohort</td>
<td>35,148</td>
<td>415</td>
<td>1.17</td>
<td>1.000 (0.874 to 1.145)</td>
</tr>
</tbody>
</table>
Group 3

Diabetes & Diabetic Retinopathy

No other risk factors
### Group 3 – Eyes from patients with Diabetes

<table>
<thead>
<tr>
<th>No PME (eyes)</th>
<th>PME (eyes)</th>
<th>Incidence (%)</th>
<th>Relative risk (and 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any DR</td>
<td>1,556</td>
<td>122</td>
<td>7.27</td>
</tr>
<tr>
<td>PRP and stable PDR</td>
<td>185</td>
<td>22</td>
<td>10.63</td>
</tr>
<tr>
<td>All PDR</td>
<td>51</td>
<td>7</td>
<td>12.07</td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>36</td>
<td>3</td>
<td>7.69</td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>190</td>
<td>21</td>
<td>9.95</td>
</tr>
<tr>
<td>Mild NPDR</td>
<td>432</td>
<td>45</td>
<td>9.43</td>
</tr>
<tr>
<td>Very mild NPDR</td>
<td>662</td>
<td>24</td>
<td>3.50</td>
</tr>
<tr>
<td>DM no DR</td>
<td>2,748</td>
<td>59</td>
<td>2.15</td>
</tr>
<tr>
<td>Reference cohort</td>
<td>35,148</td>
<td>415</td>
<td>1.17</td>
</tr>
</tbody>
</table>

**Visual acuity (logMAR)**

![Graph showing visual acuity](image)

- **Pre-op VA**: No PME: 0.6, PME: 0.7
- **<4 weeks**: No PME: 0.4, PME: 0.5
- **4 to 12 weeks**: No PME: 0.3, PME: 0.4
- **>12 to 24 weeks**: No PME: 0.3, PME: 0.4

**P = 0.02**
Diabetes – no retinopathy \( (n = \text{range 94 – 224}) \)

Incidence of Post-Cataract Surgery Cystoid Macular Oedema

(Click on a column to drill-down)

![Bar chart showing incidence of post- cataract surgery cystoid macular oedema from 2009 to 2015.](mediisoft)
Diabetes + any retinopathy \( (n = \text{range } 145 - 220) \)

Incidence of Post-Cataract Surgery Cystoid Macular Oedema

(Click on a column to drill-down)
Diabetic – > severe retinopathy (n =
• Uncomplicated cases real-world incidence is at least 1.17%.

• Visual acuity in eyes developing PME did not recover to comparable levels, even with treatment within 12-24 weeks.

• Therefore prophylaxis in high risk groups may be advisable.

• **High risk groups include:**
  • Eyes from patients with Diabetes with or without retinopathy.
  • Surgical complications including PC rupture.
  • Co-pathology including ERM, Uveitis, previous RVO and RD.

• Pre-operative topical prostaglandin analogue use is not associated with increased incidence of PME.

• Prevention better than Cure
Additional analyses needed

• Health economics analysis
  – Number of visits
  – Additional treatments
  – Visual acuity impact long-term

• Phase 2
  – Impact of NSAIDs
  – Nevanac License for Prevention of DMO in Diabetics
  – Approval by Hospital Pharmacy Boards
  – Increased use of NSAID post operatively world wide
  – Routine use of OCT
Thanks

<table>
<thead>
<tr>
<th>Name</th>
<th>Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sobha Sivaprasad</td>
<td>King's College Hospital NHS Foundation Trust</td>
</tr>
<tr>
<td>Clare Bailey</td>
<td>University Hospitals Bristol NHS Foundation Trust</td>
</tr>
<tr>
<td>Arijit Mitra</td>
<td>Sandwell and West Birmingham Hospitals NHS Trust</td>
</tr>
<tr>
<td>Atul Varma</td>
<td>Mid Yorkshire Hospitals NHS Trust</td>
</tr>
<tr>
<td>Martin Mckibbin</td>
<td>Leeds Teaching Hospitals NHS Trust</td>
</tr>
<tr>
<td>Muhammed Tahir</td>
<td>Royal Berkshire NHS Foundation Trust</td>
</tr>
<tr>
<td>Nick Lee</td>
<td>The Hillingdon Hospitals NHS Foundation Trust</td>
</tr>
<tr>
<td>Peter Scanlon</td>
<td>Gloucestershire Hospitals NHS Foundation Trust</td>
</tr>
</tbody>
</table>
When to give NSAIDs
Aim of Physicians is to prevent not Treat CMO

- **Consensus**
  - Pre-operative 1-2 days
  - But 1-2 hours may be enough
  - Post-op 3-4 weeks if no risk factors qds
  - 60 days in license
  - Once a day formulation due soon

- **Geographical variation**
  - USA Combined with steroids & antibiotics
  - Denmark used alone
Risks of NSAIDs

• Corneal complications
  – Punctate keratitis
  – Epithelial defects
  – Delayed wound healing
  – Stinging & irritation
  – Corneal infiltrates / melts

• Diclofenac, ketorolac & bromfenac – poor corneal penetration
Abstract
We describe a patient with systemic graft-versus-host disease who developed a nonhealing epithelial defect after cataract surgery that healed on cessation of a topical nonsteroidal antiinflammatory drug (NSAID) (ketorolac). The patient developed a central corneal perforation in the fellow eye while on a new NSAID formulation (nepafenac) after routine cataract surgery. Our case suggests that new topical NSAIDs may be similar to older NSAID formulations in promoting corneal melting in patients predisposed to poor epithelialization and corneal wound healing.
Claimed advantages of Nepafenac

- Nepafenac – pro-drug, rapidly penetrates cornea, ‘deaminated’ to amfenac by intraocular hydrolases
- No stinging, or burning
- RCT, double-masked, vehicle controlled study
- Patients with diabetes having cataract surgery
- CMO 3.2% vs 16.7%
- OCT (≥ 30% increase in subfield thickness)

- Clinical Trials Gov
  - Comparison of Diclofenac vs. Nepafenac Ophthalmic Drops: Patient Comfort

Singh et al. Clinical Ophthalmology June 2012, RCT, double-masked 263 diabetic patients
Clinical available NSAID’s

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Manufacturer</th>
<th>Chemical class</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketorolac</td>
<td>Acular</td>
<td>Allergan</td>
<td>Phenylalkanoic acid</td>
<td>0.5% solution</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Voltaren</td>
<td>Novartis</td>
<td>Phenylacetic acid</td>
<td>0.1% solution</td>
</tr>
<tr>
<td>Nepafenac</td>
<td>Nevanac</td>
<td>Alcon</td>
<td>Arylacetic acid</td>
<td>0.1% suspension</td>
</tr>
<tr>
<td>Bromfenac</td>
<td>Xibrom</td>
<td>Bausch and Lomb</td>
<td>Phenylacetic acid</td>
<td>0.09% solution</td>
</tr>
</tbody>
</table>
Relative Potency of NSAID
Lower is more effective NSAID

<table>
<thead>
<tr>
<th>IC_{50} COX-2 (nM)</th>
<th>IC_{50} COX-2 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromfenac 6.6</td>
<td>Bromfenac 23</td>
</tr>
<tr>
<td>Ketorolac 120</td>
<td>Diclofenac 85</td>
</tr>
<tr>
<td></td>
<td>Amfenac 150</td>
</tr>
</tbody>
</table>
## Bromfenac Side effects

<table>
<thead>
<tr>
<th>Ocular adverse events</th>
<th>Bromfenac 0.09%</th>
<th>Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>356 (100%)</td>
<td>171 (100%)</td>
</tr>
<tr>
<td>Iritis</td>
<td>7.0%</td>
<td>18.1%</td>
</tr>
<tr>
<td>Abnormal sensation in eye</td>
<td>6.5%</td>
<td>8.2%</td>
</tr>
<tr>
<td>Eye pain</td>
<td>4.2%</td>
<td>11.7%</td>
</tr>
<tr>
<td>Eye pruritis</td>
<td>3.9%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Posterior capsule opacification</td>
<td>3.9%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Partial vision loss</td>
<td>3.1%</td>
<td>9.4%</td>
</tr>
<tr>
<td>Eye irritation (burning/stinging)</td>
<td>2.5%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Eye redness</td>
<td>2.2%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>2.2%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Photophobia</td>
<td>2.0%</td>
<td>11.1%</td>
</tr>
</tbody>
</table>

Bromfenac vs ketorolac vs diclofenac for the treatment of acute pseudophakic CME

- Rho et al. presented results of a study comparing bromfenac ophthalmic solution with diclofenac and ketorolac for the treatment of acute pseudophakic CME. Sixty-four eyes with documented CME after uncomplicated cataract surgery were randomized to receive bromfenac bid, diclofenac qid, or ketorolac qid for 3 months.
- All 3 treatment groups achieved statistically significant visual improvement,
- The differences between the groups were not significant, there was a trend toward significance for the bromfenac group.
- Rho concluded that twice-daily bromfenac was statistically as effective as diclofenac or ketorolac dosed 4 times daily.

Rho DS, Soll SM, Markovitz BJ. Bromfenac 0.09% versus diclofenac sodium 0.1% versus ketorolac tromethamine 0.5% in the treatment of acute pseudophakic cystoids macular edema: diclofenac versus ketorolac. Proceedings of the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting; Ft. Lauderdale, FL. April 30–May 4, 2006; p. AF211
Conclusions

• Patient need – there is a problem with CMO
• Under-recognised
• Nepafenac
  – Licensed for diabetics having cataract surgery
  – Prevention & treatment post-op pain & inflammation
  – To treat cystoid macular oedema
  – Anecdotally great in uveitis
Post-cataract Prevention of Inflammation and Macular Edema by Steroid and Nonsteroidal Anti-inflammatory Eye Drops

A Systematic Review

Line Kessel, MD, PhD, Britta Tendal, PhD, Karsten Juhl Jørgensen, MD, DrMedSci, Ditte Erngaard, MD, Per Flesner, MD, PhD, Jens Lundgaard Andresen, MD, PhD, Jesper Hjortdal, MD, DrMedSci

Manuscript no. 2013-1766.
### CME at 1 month post surgery

**Steroids Vs NSAID**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Steroid Events</th>
<th>NSAID Events</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3.1.1 Beta- and dexamethasone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asano 2008</td>
<td>20</td>
<td>69</td>
<td>5.00 [1.80, 13.87]</td>
</tr>
<tr>
<td>Miyanaga 2009</td>
<td>1</td>
<td>23</td>
<td>3.25 [0.14, 76.01]</td>
</tr>
<tr>
<td>Wang 2013 B</td>
<td>4</td>
<td>41</td>
<td>4.50 [0.25, 79.72]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>133</td>
<td>114</td>
<td>4.77 [1.90, 11.96]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>25</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 2 (P = 0.97); I² = 0%</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect: Z = 3.33 (P = 0.0009)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **3.1.2 Fluorometholone** | | | |
| Miyake 2000          | 20             | 53           | 20.00 [2.78, 143.89]            |
| Miyake 2007          | 7              | 25           | 15.00 [0.90, 249.30]            |
| Miyake 2011          | 16             | 27           | 4.15 [1.59, 10.83]              |
| Wang 2013            | 3              | 43           | 3.34 [0.18, 61.77]              |
| **Subtotal (95% CI)** | 148           | 126          | 5.84 [2.64, 12.91]              |
| **Total events**     | 46             | 5            |                                |
| **Heterogeneity: Tau² = 0.00; Chi² = 2.96, df = 3 (P = 0.40); I² = 0%** |
| **Test for overall effect: Z = 4.36 (P < 0.0001)** |

| **Total (95% CI)** | 281           | 240          | 5.35 [2.94, 9.76]               |
| **Total events**    | 71            | 9            |                                |
| **Heterogeneity: Tau² = 0.00; Chi² = 3.00, df = 6 (P = 0.81); I² = 0%** |
| **Test for overall effect: Z = 5.47 (P < 0.000001)** |
| **Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² = 0%** |

### INTRA-OCULAR PRESSURE

#### Table 6.1.1 Beta- and dexamethasone

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Steroid Mean</th>
<th>SD</th>
<th>Total</th>
<th>NSAID Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asano 2008</td>
<td>13.27</td>
<td>3.18</td>
<td>63</td>
<td>11.39</td>
<td>2.47</td>
<td>65</td>
<td>8.4%</td>
<td>1.88 [0.89, 2.87]</td>
<td></td>
</tr>
<tr>
<td>Laurell 2002</td>
<td>15</td>
<td>2.6</td>
<td>59</td>
<td>14</td>
<td>2.7</td>
<td>55</td>
<td>8.5%</td>
<td>1.00 [0.03, 1.97]</td>
<td></td>
</tr>
<tr>
<td>Missotten 2001</td>
<td>14</td>
<td>2.6</td>
<td>74</td>
<td>13.1</td>
<td>2.7</td>
<td>71</td>
<td>9.2%</td>
<td>0.90 [0.04, 1.76]</td>
<td></td>
</tr>
<tr>
<td>Miyanga 2009</td>
<td>10</td>
<td>2.5</td>
<td>22</td>
<td>9</td>
<td>2.5</td>
<td>25</td>
<td>5.8%</td>
<td>1.00 [-0.43, 2.43]</td>
<td></td>
</tr>
<tr>
<td>Wang 2013 B</td>
<td>12</td>
<td>2</td>
<td>38</td>
<td>12.4</td>
<td>2.2</td>
<td>27</td>
<td>8.0%</td>
<td>-0.40 [-1.45, 0.65]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>256</strong></td>
<td></td>
<td><strong>243</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>39.8%</strong></td>
<td><strong>0.88 [0.16, 1.61]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.40; Chi² = 9.77, df = 4 (P = 0.04); I² = 59%
Test for overall effect: Z = 2.38 (P = 0.02)

#### Table 6.1.2 Loteprednol and prednisolone

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Steroid Mean</th>
<th>SD</th>
<th>Total</th>
<th>NSAID Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>El-Harazi 1998</td>
<td>16.7</td>
<td>1.59</td>
<td>10</td>
<td>16.58</td>
<td>1.17</td>
<td>19</td>
<td>7.5%</td>
<td>0.12 [-1.00, 1.24]</td>
<td></td>
</tr>
<tr>
<td>El-Harazi 1998 B</td>
<td>16.7</td>
<td>1.59</td>
<td>10</td>
<td>16.32</td>
<td>1.8</td>
<td>19</td>
<td>6.6%</td>
<td>0.38 [-0.90, 1.66]</td>
<td></td>
</tr>
<tr>
<td>Hirneiss 2005</td>
<td>14.6</td>
<td>2.702</td>
<td>12</td>
<td>13.73</td>
<td>1.8293</td>
<td>7</td>
<td>3.7%</td>
<td>0.87 [-1.17, 2.91]</td>
<td></td>
</tr>
<tr>
<td>Holzer 2002</td>
<td>12.7</td>
<td>4.1</td>
<td>29</td>
<td>13.7</td>
<td>3.1</td>
<td>30</td>
<td>4.2%</td>
<td>-1.00 [-2.86, 0.86]</td>
<td></td>
</tr>
<tr>
<td>Roberts 1995</td>
<td>16.56</td>
<td>2.702</td>
<td>27</td>
<td>15.26</td>
<td>1.8293</td>
<td>22</td>
<td>6.6%</td>
<td>1.30 [0.03, 2.57]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>88</strong></td>
<td></td>
<td><strong>97</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>28.6%</strong></td>
<td><strong>0.40 [-0.27, 1.08]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.07; Chi² = 4.54, df = 4 (P = 0.34); I² = 12%
Test for overall effect: Z = 1.18 (P = 0.24)

#### Table 6.1.3 Fluorometholone and rimexolone

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Steroid Mean</th>
<th>SD</th>
<th>Total</th>
<th>NSAID Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirneiss 2005 B</td>
<td>13.25</td>
<td>2.702</td>
<td>14</td>
<td>13.73</td>
<td>1.8293</td>
<td>7</td>
<td>3.9%</td>
<td>-0.48 [-2.44, 1.48]</td>
<td></td>
</tr>
<tr>
<td>Miyake 2000</td>
<td>11.85</td>
<td>3.12</td>
<td>48</td>
<td>11.37</td>
<td>2.64</td>
<td>49</td>
<td>7.3%</td>
<td>0.48 [-0.67, 1.63]</td>
<td></td>
</tr>
<tr>
<td>Miyake 2007</td>
<td>14.2</td>
<td>2.8</td>
<td>25</td>
<td>13.3</td>
<td>1.9</td>
<td>25</td>
<td>6.4%</td>
<td>0.90 [-0.43, 2.23]</td>
<td></td>
</tr>
<tr>
<td>Miyake 2011</td>
<td>10</td>
<td>2.5</td>
<td>22</td>
<td>9</td>
<td>2.5</td>
<td>25</td>
<td>5.8%</td>
<td>1.00 [-0.43, 2.43]</td>
<td></td>
</tr>
<tr>
<td>Wang 2013</td>
<td>11.3</td>
<td>2</td>
<td>43</td>
<td>12.4</td>
<td>2.2</td>
<td>27</td>
<td>8.1%</td>
<td>-1.10 [-2.12, -0.08]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>152</strong></td>
<td></td>
<td><strong>133</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>31.5%</strong></td>
<td><strong>0.14 [-0.74, 1.03]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.55; Chi² = 8.94, df = 4 (P = 0.06); I² = 55%
Test for overall effect: Z = 0.32 (P = 0.75)

**Total (95% CI)** 496 473 100.0% 0.50 [0.05, 0.96]

Heterogeneity: Tau² = 0.39; Chi² = 28.40, df = 14 (P = 0.01); I² = 51%
Test for overall effect: Z = 2.17 (P = 0.03)
Test for subgroup differences: Chi² = 1.75, df = 2 (P = 0.42), I² = 0%
Visual Acuity between two groups

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Steroid Mean</th>
<th>Steroid SD</th>
<th>Steroid Total</th>
<th>NSAID Mean</th>
<th>NSAID SD</th>
<th>NSAID Total</th>
<th>Weight</th>
<th>Mean Difference (IV, Random, 95% CI)</th>
<th>Mean Difference (IV, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asano 2008</td>
<td>-0.066</td>
<td>0.078</td>
<td>52</td>
<td>-0.071</td>
<td>0.08</td>
<td>58</td>
<td>22.6%</td>
<td>0.00 [-0.02, 0.03]</td>
<td></td>
</tr>
<tr>
<td>Endo 2010</td>
<td>-0.04</td>
<td>0.085</td>
<td>31</td>
<td>-0.09</td>
<td>0.056</td>
<td>31</td>
<td>20.6%</td>
<td>0.05 [0.01, 0.09]</td>
<td></td>
</tr>
<tr>
<td>Miyanaga 2009</td>
<td>0.07</td>
<td>0.08</td>
<td>22</td>
<td>0.1</td>
<td>0.01</td>
<td>25</td>
<td>21.3%</td>
<td>-0.03 [-0.06, 0.00]</td>
<td></td>
</tr>
<tr>
<td>Wang 2013</td>
<td>0.084</td>
<td>0.1</td>
<td>43</td>
<td>0.044</td>
<td>0.07</td>
<td>21</td>
<td>18.6%</td>
<td>0.04 [-0.00, 0.08]</td>
<td></td>
</tr>
<tr>
<td>Wang 2013 B</td>
<td>0.092</td>
<td>0.12</td>
<td>41</td>
<td>0.044</td>
<td>0.07</td>
<td>20</td>
<td>17.0%</td>
<td>0.05 [0.00, 0.10]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>189</strong></td>
<td></td>
<td></td>
<td><strong>155</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td></td>
<td><strong>0.02 [-0.01, 0.05]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 14.12, df = 4 (P = 0.007); I² = 72%
Test for overall effect: Z = 1.30 (P = 0.19)
Topical Steroids VS NSAID

- 15 Trials were identified
- High quality evidence that Post operation inflammation less in NSAID group
- 3.8% VS 25.3% !
- No adverse events in either group
- Slightly higher iop rise in Steroid group.
- Different steroids used, but no difference in effectiveness found
- 5 different NSAID but study not designed to distinguish which is the best non-steroidal anti-inflammatory
What have We done in London

- **Non – Diabetics** ALL get Bromfenac twice per day for one month post surgery since 2011

- TobraDex
  Four times a day for a week then
  Twice per day for a week and stop.

- **Diabetics** get Nevanac Pre and Post surgery for 2 months.
- Plus TobraDex
Patient Eye Drop Chart

TobraDex WEEK 1 & 2

**EYEDROP CHART AFTER OPERATION**

<table>
<thead>
<tr>
<th>Tobradex Week one Four times per day (Steroid and antibiotic)</th>
<th>Tobradex Week 2 Twice per day (Steroid and antibiotic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breakfast</td>
<td>Lunch</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Monday</td>
<td></td>
</tr>
<tr>
<td>Tuesday</td>
<td></td>
</tr>
<tr>
<td>Wednesday</td>
<td></td>
</tr>
<tr>
<td>Thursday</td>
<td></td>
</tr>
<tr>
<td>Friday</td>
<td></td>
</tr>
<tr>
<td>Saturday</td>
<td></td>
</tr>
<tr>
<td>Sunday</td>
<td></td>
</tr>
</tbody>
</table>
Audit of Post operation CME at The Hillingdon Hospital – London Fundus fluorescein angiography & OCT Proven

- Audit 2011: 14 cases of CME out of 906 cataract operations were identified in the 6-month period prior to the use of Bromfenac compared to

- 4 cases out of 838 in following 6 months. The association between CMO and bromfenac was statistically significant according to Fisher’s exact test ($P=0.03$).

- Audit 2014: No confirmed Irvine-Gass in past year in diabetics!

- WEH – 5 Cases Diabetics
  - 1 prescribed in clinic – forgot to take
  - 4 arrived at theatre None prescribed/preop
CMO case despite Nevanc

- 75 Year NIDDM,
- Previous RD Surgery
  - Intravitreal Gas
- Senior Surgeon Phaco
- Floppy Iris and Small pupil
- Anterior Capsule tear
- Prolonged surgery.

- Post operation Drops
- TobraDex and Nevanac

- Slight Distortion 4 weeks after operation
- OCT small changes and Leakage on Disc FFA.
- Vision 2 Months 0.12 same as fellow eye & No CMO
- Continues on Nevanac
Petaloid Leakage with Optic Disc leakage
PRevention of Macular EDema After Cataract Surgery (PREMED)

- 1350 Participants
- Bromfenac
- Dexamethasone QID
- Bromfenc & Dexamethasone
- Bromfenac & peroperative subconjunctival injection of 40 mg triamcinolone acetonide
- Bromfenac & Peroperative intravitreal bevacizumab
- Bromfenac & Dexamethasone & Triamcinolone & Bevacizumab

- Multi centre European Study
- sponsor Maastricht University Medical Centre
- Collaborator ESCRS
- Non diabetics over 21
- Change in Vision over time
- Change in OCT thickness
- Change in IOP

- The study is expected to complete in July 2015. [22]

More information on Clinical Trials Web site https://clinicaltrials.gov/ct2/show/NCT01774474
Dropless Cataract surgery
AA0 2015 Hot topic
Unmet need

- Compliance
  - Avoid non-compliance
- Quality of life
- Manual dexterity
  - Physical limitations eg Strokes etc
- Ocular surface toxicity
- Penetration into the eye
  - Peaks and troughs
- Elderly
  - Alzheimer's – Forgetting drops
  - Simplifies Post op Regime
Dropless Cataract surgery
AA0 2015 Hot Topic
Benefits of Intraocular Antibiotics and Steroids

- High Effective prophylaxis against infection
- Pre-Emptive control of inflammation
- Greater patient Convenience
- Better Compliance
- Less cost?

- Number of Options being trialed
  - Subtenons Kenalog – 10 – 40mg
    - IOP issues, but inexpensive
    - Available to all – rarely used
  - Triamcinolone & Moxifloxacin = TriMoxi or TriMoxVanc
    - Compounding pharmacy – USA
  - OTX-DP
    - Dexamethasone Punctal Pellet
  - IBI-10090 Dexmatheasone Suspesion
    - Anterior chamber bioabsorbable Dexamethasone
Transzonular medicine

- This is the injection of drugs via the anterior approach through the zonules.
- Idea is to avoid the need for post op drops entirely.
- Early trials encouraging.
- TriMoxi (triamcinolone acetonide and moxifloxacin hydrochloride, Imprimis Pharmaceuticals) and TriMoxi+Vancomycin (Imprimis Pharmaceuticals) use patent-pending technologies that allow for the combination of drugs into a single, cost-effective intraocular injection.
- “A retrospective analysis including data from a consecutive series of 1575 eyes shows that intravitreal placement of triamcinolone/moxifloxacin during cataract surgery is a safe and effective method for preventing inflammation, endophthalmitis, and cystoid macular edema.”
• Prepared by a compounding pharmacy, the preservative-free product contains 15 mg triamcinolone +1 mg moxifloxacin per mL. A dose of 0.2 mL is placed into the anterior vitreous after IOL implantation and prior to viscoelastic removal using a 27-gauge cannula passed through the zonules via the ciliary sulcus inferiorly.

• None needed more steroids but 22% needed a NSAID due to high risk of CMO.

**Visual Acuity**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same Day ≤ 20/100</td>
<td>51%</td>
</tr>
<tr>
<td>P3 UCVA ≥ 20/40</td>
<td>78%</td>
</tr>
<tr>
<td>P3 UCVA ≥ 20/25</td>
<td>37%</td>
</tr>
<tr>
<td>P3 BCVA ≥ 20/40</td>
<td>96%</td>
</tr>
<tr>
<td>P3 BCVA ≥ 20/25</td>
<td>79%</td>
</tr>
</tbody>
</table>

By 3 weeks, best-corrected visual acuity was 20/40 or better in 96% of eyes and 20/25 or better in 79%.

**CME Incidence**

<table>
<thead>
<tr>
<th>Category</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>2</td>
</tr>
<tr>
<td>Low Risk</td>
<td>1.5</td>
</tr>
<tr>
<td>High Risk</td>
<td>3.5</td>
</tr>
<tr>
<td>High Risk + NSAID</td>
<td>1.9</td>
</tr>
<tr>
<td>DM</td>
<td>2.7</td>
</tr>
<tr>
<td>ERM</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Not all high-risk eyes were prescribed supplemental treatment with a topical nonsteroidal anti-inflammatory drug, but the incidence of cystoid macular edema was only 1.9% in those eyes that were. (Figures courtesy of M. Stewart Galloway, MD)
AA0 2015 Topical Steroids vs NSAID
Transzonular medicine
Ahad Mahootchi

- Comparative case series 415 per group 1245 total number
- 90 Day follow up
- Group 1 – Standard care Steroids and NSAID 1.9%
- Group 2 – Transzonular and Post op steroids 1.9%
- Group 3 – Transzonular and NSAID 0% (0.5%)
A Phase 3 Trial of a Novel Intracameral Dexamethasone Drug Delivery Suspension for Treating Inflammation Following Cataract Surgery

Eric Donnenfeld, MD
Clinical Professor of Ophthalmology, New York University
Trustee Dartmouth Medical School
Edward Holland, MD
Wendy Murahashi, MD
for the C13-04 Study Investigators
IBI-10090 Dexamethasone Suspension for Intraocular Administration

- A novel, bioabsorbable drug delivery product for anterior chamber intracameral placement of dexamethasone
- Therapeutic levels are maintained for up to 21 days with a single administration
- Evaluated in a Phase 3 trial for treatment of inflammation associated with cataract surgery

Patients Requiring Rescue Medication

<table>
<thead>
<tr>
<th>Postoperative Day</th>
<th>Placebo N=80</th>
<th>IBI-10090 342 µg N=158</th>
<th>IBI-10090 517 µg N=156</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 (7.5%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>14 (17.5%)</td>
<td>0</td>
<td>4 (2.3%)</td>
</tr>
<tr>
<td>8</td>
<td>13 (16.3%)</td>
<td>3 (1.9%)</td>
<td>3 (1.9%)</td>
</tr>
</tbody>
</table>
Primary Endpoint
Percentage of Patients With ACC Grade=0 at Day 8

- Placebo: N=80, 25.0%
- IBI-10090 342 µg: N=158, 63.1%
- IBI-10090 517 µg: N=156, 66.0%
Phase 3 Clinical Trials Evaluating Sustained Release Dexamethasone (DEXTENZA™) for Treatment of Post-operative Inflammation and Pain

Thomas Walters, MD
Texan Eye, Austin, TX

Phase 3 Studies Conducted under IND
Sponsored by Ocular Therapeutix, Inc.
OTX-DP Product Design

- Polyethylene glycol-based hydrogel drug product
- Provides a sustained and tapered release of dexamethasone to the ocular surface for up to 30 days
- One-time administration at the conclusion of surgery
- Fluoresces under blue light and yellow filter for placement and retention confirmation
- Resorbs and exits the nasolacrimal system; removal not required
Conclusions

- Strong safety profile shown for OTX-DP in both studies - No safety concerns
- OTX-DP was statistically superior over placebo for the absence of pain at Day 8 for both studies
- OTX-DP was statistically superior over placebo for the absence of Anterior Chamber cells:
  - In the first Phase 3 study
  - Not in the second Phase 3 study
- NDA for pain indication submitted to FDA
- Conducting third Phase 3 study to expand labeling to include inflammation
Old Practice  - Eye drops four times an hour, then every half hour by nurses

Current Practice  - Mydriasant Pellet
- Slow and sustained
- Maximal Dilatation

Future practice  - Intracameral on the table
- Tropicamide, Phenylephrine, & Lidocaine
- Less dilation, but continues
- Fast 20 Seconds

Improved patient flow, Less waiting for patient Less discomfort

Mydriatic insert and intracameral injections compared with mydriatic eyedrops in cataract surgery: Controlled studies
Journal of Cataract and Refractive Surgery.
Dropless Cataract surgery
AA0 2015 Hot Topic
Benefits of Intraocular Antibiotics and Steroids

• High Effective prophylaxis against infection
• Pre-Emptive control of inflammation
• Greater patient Convenience
• Better Compliance
• Less cost?

• Number of Options being trialed
  – Subtenons Kenalog – 10 – 40mg
  – Trans Zonular Triamcinolone & Moxifloxacin
  – OTX-DP Dexamethasone Punctal Pellet
  – IBI-10090 Dexmatheasone Suspension Intracameral
The Future Pathway

- Walk in, Theatre, walk out – 1 hour
- On table Intracameral Dilatation
- On table Intercameral Antibiotic – Cefuroxime – Others?
- On Table Long acting Steroid
- NSAID  Once a day Gel
Make Irvine-Gass a Complication of the past
Use a NSAID

More information
EyeNews
“A Paradigm shift in the way we approach Cataract Surgery”

www.nicholaslee.co.uk
NEVANAC Prescribing Information
(Refer to full Summary of Product Characteristics (SmPC) before prescribing)
Presentation: 1 ml of Nevanac suspension contains 1 mg nepafenac, benzalkonium chloride 0.05 mg. Indication(s): Prevention and treatment of postoperative pain and inflammation associated with cataract surgery. Reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients. Posology and method of administration: Adults, including the elderly: For the prevention and treatment of pain and inflammation, 1 drop in the affected eye(s) 3 times daily beginning 1 day prior to cataract surgery, continued on the day of surgery and up to 21 days of the postoperative period, as directed by the clinician. An additional drop should be administered 30 to 120 minutes prior to surgery. For the reduction in the risk of macular oedema associated with cataract surgery in diabetic patients, 1 drop in the affected eye(s) 3 times daily beginning 1 day prior to cataract surgery, continued on the day of surgery and up to 60 days of the postoperative period, as directed by the clinician. An additional drop should be administered 30 to 120 minutes prior to surgery. Children and adolescents: Not recommended. Hepatic and renal impairment: No dose adjustment warranted. Contra-indications: Hypersensitivity to nepafenac, any of the excipients, or to other nonsteroidal anti-inflammatory drugs (NSAIDs); and in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs. Warnings and precautions: Do not inject, or swallow. Instruct patients to avoid sunlight during treatment. Use of topical NSAIDs may result in keratitis, in some susceptible patients, continued use may be sight threatening. Topical NSAIDs may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems. Topical NSAIDs should be used with caution in patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases, rheumatoid arthritis or repeat ocular surgeries within a short period of time. These patients may be at increased risk for corneal adverse reactions which may become sight threatening. Prolonged use of topical NSAIDs may increase patient risk for occurrence and severity of corneal adverse reactions. Ophthalmic NSAIDs may cause increased bleeding of ocular tissues (including hyphaemas) in conjunction with ocular surgery. Use NEVANAC with caution in patients with known bleeding tendencies or who are receiving other medicinal products which may prolong bleeding time. Concomitant use of prostaglandin analogues and NEVANAC is not recommended. Benzalkonium chloride may cause keratopathy and irritation and is known to discolour soft contact lenses. Contact lens wear is not recommended during the postoperative period following cataract surgery. Patients should be advised not to wear contact lenses during treatment with NEVANAC. Close monitoring is required with frequent or prolonged use. An acute ocular infection may be masked by the topical use of anti-inflammatory medicines. NSAIDs do not have any antimicrobial properties. In case of ocular infection, their use with anti-infectives should be undertaken with care. Cross-sensitivity: Potential exists for cross-sensitivity of nepafenac to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs. Interactions: In vitro studies have demonstrated a very low potential for interaction with other medicinal products and protein binding interactions. Pregnancy and lactation: Pregnancy: not recommended during pregnancy and in women of childbearing potential not using contraception. Lactation: Can be used during lactation. Effects on ability to drive and use machines: If blurred vision occurs wait until the vision clears before driving or using machinery. Undesirable effects: Common: Punctate keratitis. Frequency not known: Dizziness, impaired corneal healing, corneal scar, reduced visual acuity, eye irritation, eye swelling, blood pressure increased. Serious: Keratitis, choroidal effusion, corneal epithelium defect, corneal opacity. Prescribers should consult the SmPC in relation to other side effects. Overdose: No experience of overdose with ocular use. Application of >1 drop/eye is unlikely to lead to unwanted sideeffects. Practically no risk of adverse effects due to accidental oral ingestion. Incompatibilities: Not applicable. Special Precautions for Storage: Do not store above 30°C. Legal Category: POM. Package Quantities and Basic NHS Costs: 5ml & 14.92. MA Number(s): EU/1/07/433/001. Further information available from the MA Holder: Alcon Laboratories (UK) Ltd. Frimley Business Park, Frimley Camberley, Surrey, GU16 7SR United Kingdom. Date of preparation: 20 May 2013 (V9). Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Alcon Medical Information. Tel: 0871 376 1402. Email: GB.ADR@alcon.com © 2014