New Methods for Steroid Delivery in Sinus Disease

Andrew H. Murr, MD FACS
Professor
Chief of Service
Department of Otolaryngology/Head and Neck Surgery
San Francisco General Hospital

Roger Boles, M.D., endowed chair in otolaryngology education
Department of Otolaryngology-Head and Neck Surgery
University of California, San Francisco School of Medicine

Disclosure

- Consultant for IntersectENT
- Stockholder

Scope of the Problem: Sinusitis

- 16% of adults in the U.S.A.
  - 17% U.K.
  - 13.5% Canada
- 4.8 missed days of work/year
- $1539 per patient per year
- Annual per patient medication cost: $1200
- 250,000 ethmoidectomies/year

Definition of Sinusitis

- Chronic Sinusitis
  - With Nasal Polyps
    - Easy to recognize: CT or Endoscopic Exam
  - Without Nasal Polyps
    - Time based: 8 – 12 weeks
Treatment of Nasal Polyps

- Antibiotics
- Antifungals
- Corticosteroids
- Anti-Leukotrienes
- Antihistamines
- Mast cell stabilizers
- Parasympathetic blockade drugs
- Surgery

Corticosteroid Delivery

- Topical
  - Spray
  - Irrigation
- Systemic
- Direct injection

Evidence: Topical Delivery


"This systematic review showed that intranasal steroids decrease polyp size, which we believe would provide some relief of nasal obstruction."
Evidence: Topical Steroids in CF

Evidence: Topical Steroids Larger Dose

<table>
<thead>
<tr>
<th>Study or reference</th>
<th>Steroid dose</th>
<th>Placebo</th>
<th>No. Pat</th>
<th>No. Pat</th>
<th>N/A</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 7 yr in France</td>
<td>100 µg</td>
<td>72/24</td>
<td>12/10</td>
<td>12/10</td>
<td>7.74 7.8 ± 1.1 7.7 ± 1.1</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.7 ± 1.1</td>
<td></td>
</tr>
</tbody>
</table>

Evidence: Topical Steroids Larger Dose

Evidence: Topical Steroids Larger Dose
Evidence: Budesonide (Pulmicort) Respules


Does Budesonide in Respule Nasal Washes cause Adrenal Cortex Suppression?


Systemic Steroid Delivery

- Cochrane Database 2011 Jul6;(7):CD005232
- “The authors found three randomised controlled trials [166 patients], albeit of moderate to poor quality, that suggest a short-term benefit of oral steroids in patients with multiple nasal polyps. To address the issue more thoroughly well-designed, prospective, randomised controlled trials are still needed.”
- Parameters:
  - Polyp size (endoscopic)
  - Symptom questionnaires
  - QOL
Steroid Injection of Nasal Polyps


- 1495 Injections, 358 patients:
  - Medical treatment (14%)
  - Medical treatment and injection (19%)
  - Medical treatment and surgery (33%)
  - Medical treatment, injection, surgery (34%)
- 26 Surgical complications, 1 injection complication (diplopia)
- .5 – 1cc of a 50:50 mixture of triamcinolone acetonide suspension [Kenalog 40] with 1% lidocaine with epinephrine 1:100,000
- Injection appeared to decrease frequency of surgery
- No evidence presented related directly to efficacy

New Methods of Longer Term Deposition of Steroids

- Steroid infused carboxymethylcellulose foam
- Bioabsorbable steroid eluting stent

Deposited Steroid Delivery

- Carboxymethylcellulose
  - High viscosity foam
    - CMC = carboxymethylcellulose
    - Injectable dressing
    - Platelet aggregation
  - Mixed with 8cc of sterile water
  - Can be mixed with 8 cc of Triamcinolone acetonide
    - 40mg/cc
    - Total dose of 160 mg of triamcinolone per side

Advantage of Deposited Steroid

- Excellent delivery localization because placed directly in ethmoid cavity under direct vision
- Higher dose of steroid than currently available commercially for topical use
- No patient compliance required
- Avert systemic steroid toxicity compared to large oral doses
Study Design

- 8 patients with CRS with Nasal Polyps
  - Undergo FESS with recurrence/persistence

- Pre-treatment Data
  - SNOT 20
  - POSE
    - Peri-operative sinus endoscopy score
    - Synchie category deleted
  - VAS

Study Design

- All patients had previous surgery
- All patients failed aggressive post op steroid regimens
- 8 cc of Carboxymethylcellulose foam admixed with 8 cc Triamcinolone acetonide, 40mg/ml
- 4 cc placed in each ethmoid cavity
- Cease irrigation x 48 hours

Study Endpoints

- POSE scoring
  - Before treatment
  - 1 week
  - 1 month
- SNOT-20
  - Before treatment
  - 1 week
  - 1 month
- VAS

Carboxymethylcellulose and Triamcinolone

Pletcher, M.I. Goldberg, A.N. Treatment of recurrent sinonasal polyposis with steroid-infused carboxymethylcellulose foam. Am J Rhinol Allergy. 2010

PubMed PMID: 21144224
**Limitations**

- Subjective nature of endoscopic scoring as an endpoint
  - Validated scoring scales
- CMC foam itself may be so beneficial that adding steroid to it will not elevate its effect beyond using it as designed
  - Clinical impression is otherwise
  - If this is so, then it is helpful to know that we should not utilize the product in this way

**Potential Benefit**

- Utilizing deposited CMC/triamcinolone acetonide in this manner may obviate the need for oral steroid delivery in the post operative period
- Potentially greater convenience for the patient
- Ability to use this technology in the clinic setting

**Bioabsorbable Steroid Eluting Stent**

**Background**

- Principles of FESS center around:
  - Reversibility of mucosal disease
  - Atraumatic surgical technique
  - Careful post-operative assessment and control of disease
Causes of FESS Failure

- Recurrent inflammation
- Recurrent polyps
- Adhesion/synechia formation
- Middle turbinate lateralization
- Stenosis of surgically created ostia

Devices: Counteract Stenosis/Adhesions/Scar

- Packing
- Stents
- Sponges
- Gels

Inflammation Control

- Antibiotics
- Corticosteroids
  - Topical
  - Systemic
    - Oral
    - Intravenous
- Antihistamines
- Mast Cell Stabilizers
- Anti-leukotriene drugs
- NSAID

Bioabsorbable Steroid-Eluting Stent Device

- Stent
  - Spring-like design
  - Polylactide-co-glycolide
- Mometasone Furoate
  - Gradually released over approximately 30 days
  - 370 micrograms
  - FDA approved spray
    - 100 micrograms/day A.R.
    - 200 micrograms/day Polyps
**Example of Stent Placement**

**Study Design**

- Prospective, multi-center, randomized, double blind, controlled clinical trial
  - Patients undergoing FESS for CRS refractory to medical management of 3 months duration or more
  - With or without Nasal Polyps
  - Primary or revision surgery
  - Intra-patient control design
  - Oral steroids not permitted in a 14 day run-in
  - IV steroids given perioperatively
    - 4mg – 20 mg
  - No post operative steroids until Day 30
  - 14 Day course of Amoxicillin with Clavulonic Acid begun one day preoperatively
  - Saline spray permitted throughout

**Patient Enrollment**

- 4 Centers
- Adults
- CT
  - Minimum Lund-Mackay of 6 (> or = 3 per side)
- Bilateral Ethmoidectomy
  - Bilateral MMA
  - with or without septoplasty
- Randomization of Stents
  - Treatment and control stents were identical in appearance
  - Envelope method

**Follow-up Paradigm**

- POD
  - 7
  - 14
  - 21
  - 30
  - Steroid prescription allowed at this juncture if necessary by clinical opinion of treating physician
  - 45
  - 60

![Follow-up Paradigm Diagram](image)
Efficacy Assessment

- Inflammation graded on 10 cm VAS
- Middle Turbinate Position
  - 4 point scale
    1. Medialized
    2. Normal
    3. Partially lateraled
    4. Lateralized
- Adhesion Formation
  - 5 point scale
    1. None
    2. Small/non obstructing
    3. Obstructing/easily separated
    4. Dense/obstructing/difficult to separate
    5. Severe complete adhesion of MT to LNW
- Polypoid Mucosal Change
  - 5 point scale (Meltzer/Hamilos)

Efficacy Assessment Form

<table>
<thead>
<tr>
<th>Inflammation</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Moderate</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Mild</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Trace</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Polyoid Change

<table>
<thead>
<tr>
<th>Middle Turbinate Position</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medialized</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Normal</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Partially lateraled</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Lateralized</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Severe complete adhesion</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

Safety Assessment

- Cohort of 5 patients given bilateral steroid coated stents
- No steroids of any type 14 days before and 30 days after surgery
- Blood sampling (prior to surgery and days 7,14,21,30)
  - Plasma Mometasone Furoate
    - UPLC/MS/MS method of quantification
      - 30 – 2000 pg/ml
  - Plasma cortisol
    - ELISA Assay

Results: Safety

- No evidence of systemic steroid absorption
- No evidence of adrenal-pituitary axis suppression
Results

Table 1: Baseline Demographics and Clinical Information

<table>
<thead>
<tr>
<th>N=43 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male; n (%)</td>
</tr>
<tr>
<td>Age; mean (min, max)</td>
</tr>
<tr>
<td>Most common symptoms (n, %)</td>
</tr>
<tr>
<td>Nasal obstruction/congestion</td>
</tr>
<tr>
<td>Facial pain / pressure</td>
</tr>
<tr>
<td>Anosmia</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Prior FESS (n, %)</td>
</tr>
<tr>
<td>Polyps present (n, %)</td>
</tr>
<tr>
<td>OT Stage Total (L, R)</td>
</tr>
</tbody>
</table>

Table 2: Procedural Information

<table>
<thead>
<tr>
<th>Procedure</th>
<th>N (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethmoidectomy</td>
<td>43 (100%)</td>
</tr>
<tr>
<td>Sphenoidotomy</td>
<td>25 (58%)</td>
</tr>
<tr>
<td>Frontal sinusotomy</td>
<td>20 (47%)</td>
</tr>
<tr>
<td>Middle nasal antrostomy</td>
<td>42 (97%)</td>
</tr>
<tr>
<td>Middle turbinate reduction</td>
<td>8 (14%)</td>
</tr>
<tr>
<td>Septoplasty</td>
<td>14 (33%)</td>
</tr>
</tbody>
</table>

Results: Inflammation

- Day 21 p = .0032
- Day 30 p = .0011
- Day 45 p = .0022

Inflammation Assessment

Polypoid Change, Adhesion, Middle Turbinate Position

Figure 6. Mean ethmoid sinus inflammation scores over time. Error bars are 95% confidence intervals for the means. A repeated measures GEE model tested whether inflammation scores were different. Differences indicated by * are statistically significant (p < 0.05).
Bioabsorbability

Discussion

• Function of the Stent
  – Mechanical function
    • Spring like mechanical function
    • Patency of ethmoid cavity
  – Pharmacological function
    • Systemic steroid side effects obviated
    • Decreased polyp formation and inflammation
    • Improves mechanical function of stent
      – Adhesions/stenosis
  – Bioabsorbable
    • Li, Downie, Hwang, AJR, 2009;23:591-596
      PMID 19958608

Efficacy Assessment

• No current instrument to assess changes of this nature over time
  – POSE and Lund-Kennedy do not assess turbinate position or inflammation with sufficient sensitivity
  – Goal was to show a side to side difference
    • Intra-patient control design
• Post operative CT not feasible
  – Ethics
  – Cost
• Newly developed assessment tool
  – Hybrid
  – Good inter-rater reliability
• Endoscopic Assessment provides Prognostic Information
  – Kennedy, Wright, Goldberg, Laryngoscope, 2000;110(suppl 94):29-31
  PMID 10718412

Benefit of Steroid Elution

• Adhesion rate with steroid: **5.3%**
• Adhesion rate without steroid: **21.1%**
• \( p=0.0313 \)
• Historical Comparison
  – Wormald et al., AJR, 2006 Jan-Feb; 20(1):7-10
    PMID 16539287
    • Hyaluronic Acid (HA) Packs to No packing
    • HA adhesion rate 21%
  – Miller and Steward, Oto-HNS, 2003;128:862-869
    PMID 12825038
    • HA to non absorbable packing: 35% overall with adhesions, each group similar (~25%)
    • 19% required surgical (in office) intervention
What is the Added Benefit of Steroid Elution?

- Avoid systemic steroid side effects
- Avoid inefficient aerosolized steroid delivery
  - G.I. tract shunting or non-physiologic sinus deposition
- Decreasing polyps and inflammation will decrease the need to take supplemental oral steroids in the post operative period
  - Prescriptions for steroids at Day 30 in our study were 6 times more likely to be written for patients with polyps.

Conclusion

- SAFE
- STATISTICALLY SIGNIFICANT IMPROVEMENTS
  - INFLAMMATION
    - DAYS 21-45
  - POLYPOID CHANGE
    - THROUGH DAY 30
  - SIGNIFICANT ADHESION
    - THROUGH DAY 30
Future Projects

• 1. Validate Scoring form
  – Video scoring
• 2. Further clinical studies enrolling close to 300 patients
• 3. Product pipeline

CONCLUSION