Topical Therapy for Chronic Rhinosinusitis

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Disclaimers
- No Disclosures
- Off-label use of multiple steroid and antibiotic medications
- Large talk, limited time

The Problem ...

Topical Therapy

Mode of Delivery – Sinus Distribution
- Spray
- Nebulizer
- Irrigation
- Direct/Endoscopic Application

Mechanism of Action
- Antimicrobial
- Anti-inflammatory
- Detergent
Evidence for Sinus Distribution

- 8 healthy adults
- Irrigation vs. Nebulizer
- Radio-opaque contrast material
- Coronal CT imaging after application of contrast

- Irrigation provides significantly increased distribution in maxillary and ethmoid sinuses
- Poor distribution to frontal and sphenoid sinus with all techniques

- Small sample
- Healthy controls
- No prior surgery
Irrigation Studies

- Does nasal irrigation enter paranasal sinuses in chronic sinusitis?
  - Snidvongs et al; AJR 2008
  - NO!

- Patients with CRS after ESS
- Seven subjects, dilute blue food dye
- Videoendoscopy after irrigation/spray
- Blinded grading of endoscopy videos

- Atomizer = Spray bottle
- Bulb syringe > Nebulizer at all sinuses
- Bulb syringe > Spray in ethmoid sinuses
- Cadaver study using Gastroview
- Washout with saline between evaluations
- No Surgery vs. ESS vs. Endoscopic Medial Maxillectomy

**Sinus Distribution**

- Irrigation superior to nebulizer
  - Combination irrigation/nebulizer treatments lack published data
- Disease state and endoscopic sinus surgery impact sinus distribution
Topical Therapy

- Antimicrobial
  - Antibiotic
  - Antifungal
- Anti-inflammatory
- Detergent

Review of both antibacterial and antifungal topical treatments
Examined 14 studies since 1949

AJR 2008

- Only randomized, controlled studies looked at Amphotericin B
- Conflicting results
- Antibiotic studies lower level of evidence

Conclusions
- “Emerging evidence suggesting topical antibiotics may be useful”
  - Based on Level III evidence
- Stronger evidence for culture-directed studies in post-surgical patients
- Sprays are not effective
Nasal Lavage With Mupirocin for the Treatment of Surgically Recalcitrant Chronic Rhinosinusitis

- 0.05% Mupirocin in Lactated Ringer
- Irrigate 100ml/nostril twice daily
- 16 patients
  - All with culture-proven staph aureus
  - All with prior surgery

Endpoints: Endoscopy, Symptom Score, Microbiology

Results
- Statistically significant improvement in endoscopy and symptom scores
- 15/16 swab demonstrated no staph aureus

No control group
- Subjects did irrigate for at least 3 weeks with saline prior to start of study

Biofilms?
■ Tobramycin 80mg/L -> 400 mg/L
■ Rabbit model of pseudomonas sinusitis
■ Increasing doses of tobramycin eradicated pseudomonas in lumen of sinus but did not significantly impact bacteria attached to mucosa
■ Irrigation effective against bacteria in planktonic state, but not against bacterial biofilms

Gentamicin Toxicity Studies
■ 80mg/ml irrigations of Gentamicin
■ 30 cc irrigation bilaterally bid
■ Blood gentamicin levels sent at completion of treatment (mean 7 weeks)

Whatley et al. AJR 2006

■ 10/12 patients with detectable gentamicin levels in peripheral blood
■ 4 patients with blood level in the range for gentamicin trough measurement
■ No detectable change on audiogram
■ No subjective hearing loss

Whatley et al. AJR 2006

■ Demonstrated in vitro efficacy of topical mupirocin on S. Aureus biofilms
■ F/U study in Sheep model suggested efficacy of mupirocin irrigations in the treatment of biofilm associated frontal sinusitis
■ Le et al AJR 2008
In Vitro study evaluating the affects of manuka and sidr honey on S. Aureus and P. Aeruginosa biofilms

Noted bacteriocidal effect on bacteria in planktonic and biofilm state

Rate of biofilm susceptibility ranged from 60-90%

Single-blind study of manuka honey in allergic fungal rhinosinusitis.

J Otolaryngol Head Neck Surg 2011

34 patients with AFS treated with 1:1 honey:saline irrigation for 30 days

No significant difference in endoscopy score pre and post-treatment

Antifungal Irrigations
Irrigation with 20cc of Amphotericin B 250ug/ml in each nostril for 6 months

Primary outcome measure: change of mucosal thickening on CT scan

Secondary outcome measures: endoscopy score, SNOT-20, inflammatory markers

- Initial goal was to recruit 70 patients
- 30 patients recruited for study
- 24 completed study, 5 drop-outs in Ampho group, 1 in placebo group

2 of 10 patients (20%) in Ampho group received oral prednisone for asthma exacerbation, none in placebo group received steroids

8.8% reduction of mucosal thickening in Ampho group vs. 2.5% increase in placebo group (p<.030)

Pilot study demonstrated 30% reduction in mucosal thickening with Amphotericin (13 patients)
Results

- Endoscopy score improvement was greater in treatment group ($p=0.038$)
- Both groups with slight improvement of SNOT-20 but no difference between ampho and placebo groups
- Conclude that larger, multicenter trial warranted

Multicenter randomized, double blind trial
- 25cc irrigation Amphotericin B 100ug/ml (30-100x MIC) vs. placebo for 3 months
- Enrolled 116 patients, 99 completed trial
- Equal drop-out rate between ampho and placebo groups

Outcome measures

- Visual analogue scale for multiple CRS symptoms
- RSOM-31, SF 36
- Endoscopy Scale
- Peak inspiratory nasal flow

Results

- No significant difference between groups for any outcome measure
- Trend towards worsening in Ampho group
Topical Steroid Treatment

- Meta analysis of six studies looking at topical nasal steroid sprays as a treatment for CRS with polyps
- Noted modest improvement in polyps size with
- Sprays often used at dosing regimens above FDA approval level

- Randomized, placebo-controlled, double-blind study
- Patients with CRS treated with mometasone nasal spray
- Noted significant improvements in patients symptoms in treatment group

- Exclusion criteria
  - Lund McKay CT score >10 (out of 24)
  - Visible polyps on nasal endoscopy
  - Prior sinus surgery
  - Results not applicable to patients with moderate to severe CRS
Randomized, placebo controlled, double blind study of patients scheduled for sinus surgery

- Fluticasone propionate nasal drops
  - 200ug/0.2ml each side
  - 12 week treatment course

Delivered in head back position
- Position maintained for 2 minutes after application
- 54 patients
- Majority (>80%) with prior surgery

Outcome measures
- Progression to Surgery
- VAS for multiple symptoms
- CT score
- Peak nasal inspiratory flow

Results
- Greater improvement in nasal blockage (p<.001) and rhinorrhea (p<.03) in treatment group
- CT score improved in treatment and placebo groups
- No significant difference between groups
13/27 patients in treatment group did not proceed with surgery, 6/27 in placebo group decided not to proceed with surgery (p=.046)

9 patients
0.25 mg in 5 cc saline/side
- Administered in with multiple head positions
- 30 day treatment
- Majority of patients with prior surgery

Results
- No change in cortisol levels or cortisol stimulation
- Statistically significant improvement in SNOT-20 score
- Similar findings in 2 subsequent studies
  - Welch et al AJRA 2010

Randomized, placebo-controlled double-blind study
- Patients packed with absorbable packing and 2cc kenalog 40 (treatment) or saline (placebo)
- Left and right side randomized to receive placebo or treatment
• 19 Patients
• Statistically significant improvement in endoscopy scores both short (1, 2 weeks) and long (3, 6 months) term

Patients with recurrent polyp disease after surgery treated with endoscopic application of kenalog 40 (4cc/side) infused CMC gel
• 10 treatments (20 sides)
• Pre and post treatment endoscopies randomized and graded by blinded reviewer

Videoendoscopy Scores

Symptom Scores
Review of 8 randomized controlled trials for patients with symptoms of chronic sinusitis

Children and adults

No formal diagnosis of chronic rhinosinusitis required

Saline better than no treatment for improving symptoms and disease specific quality of life scores

No difference was found in comparison of isotonic to hypertonic saline
Saline improves disease specific quality of life scores as an addition to oral antihistamine therapy.

Saline did not improve disease specific quality of life scores over a reflexology control.

Baby Shampoo Irrigations

- Symptomatic patients with prior ESS
- 1% solution of baby shampoo in Saline BID for 4 weeks
- 18 patients
- 2 discontinued due to nasal/skin irritation

Baby Shampoo Irrigations

- 47% with overall improvement in symptom score
- Thickened mucus and postnasal drainage most likely to be improved
- No control group

Chiu et al AJR 2008
NEW Warning - SinuSurf® August 3, 2011

Re: SinuSurf® Product (UPC # 705928500013) Withdrawal/Relabeling – Physician Action Required

Dear Doctor:

We write to advise you that our company is withdrawing its currently labeled SinuSurf® product for re-labeling ...

SINUSURF® should not be used more than once a day for 5 consecutive days. If you experience any side effects described above (nasal burning, decreased sense of smell, etc.), stop use immediately, and contact your physician as well as contact the medical division of our office. Do not resume use unless directed by your physician.

What I Do

- Culture-directed antibiotic Irrigations
- Baby shampoo or other detergent
- Frequent debridements

What I Do

- Budesonide 0.5mg/120cc saline
- CMC foam with kenalog
**Future Directions**

- Topical therapy will play a critical role in managing CRS
- Development of new methods of topical medication delivery
- Probiotics?

**Summary**

- Topical therapy may be helpful in patients with chronic sinusitis
- Irrigation devices demonstrate better sinus distribution than nebulizers or sprays
- Topical treatments more likely to be effective in patients with prior surgery

**Summary**

- Topical antibiotics more likely to be effective when guided by cultures
- Drug-eluting packing materials likely to play an increased role in the future

**THANK YOU**