Q2RESEARCH PROTOCOL TEMPLATE
INVESTIGATOR INITIATED TREATMENT TRIALS

Title of Project: Treatment of Post-Operative Sinonasal Polyposis with Topical Furosemide

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Co-Investigators: Gregory Epps MD, Otolaryngology; Marc Rosen, MD, Otolaryngology; Gurston Nyquist, MD, Otolaryngology;Jason Jerusik PharmD

Abstract

Prior studies have suggested that topical furosemide may reduce the recurrence of sinonasal polyposis following sinus surgery.[1,2,3] This project aims to further investigate that claim through a blinded randomized controlled clinical trial following patients who undergo functional sinus surgery for chronic rhinosinusitis with sinonasal polyposis (CRSwP) by randomly assigning participants to receive topical furosemide versus placebo nasal irrigation for 6 weeks post operatively. Outcomes would be compared at 6 months through endoscopic grading scores using Lund Kennedy and Meltzer scores as well as Sino-Nasal Outcome Test (SNOT-22) scores to measure the rate and degree of recurrence and impact on symptoms in the treatment group versus placebo.

A. Specific Aims

State the hypothesis and specific aims. List the long-term objectives and what the proposed research will accomplish.

Hypothesis: Topical furosemide prevents the recurrence of sinonasal polyposis following endoscopic sinus surgery in CRSwP patients

Through investigating this hypothesis, the group aims to provide evidence for treating CRSwP patients with a safe and effective medical therapy to prevent or reduce the recurrence of sinonasal polyposis after sinus surgery. If proven effective in the immediate post operative period, the research would lead to further research aimed at the long term effects of therapy in CRSwP patients to develop a protocol to prevent the recurrence of sinonasal polyps and potentially change the post-operative management of CRSwP patients.

B. Background and Significance

Nasal polyposis is a common disease of the mucous membranes in the nose and the paranasal sinuses that develops as a reaction to a variety of stimuli including allergens and various microbes.[4] They usually occur in chronic rhinosinusitis associated with allergy, inflammation, and submucosal edema.[5] Nasal polyps are associated with nasal congestion, postnasal drip, runny nose, sneezing and olfactory disorder that greatly impact patient's quality of life.[6] Management of nasal polyposis in this patient population is extremely difficult and functional endoscopic sinus surgery remains a mainstay of treatment in those patients who

have failed medical therapy. That said, there are high rates of recurrence after surgery.[7] Recent studies have suggested that nasal furosemide may be effective in reducing the recurrence of polyps after sinus surgery by affecting inflammation and edema post operatively.[1-3] However, evidence is limited and insufficient with further investigations required. This study aims to provide evidence for treating CRS patients with a safe and effective medical therapy to prevent or reduce the recurrence of sinonasal polyposis after sinus surgery and limit the morbidity of their recurrence in this group of patients as well as the limit the risks of corticosteroid steroid therapy used currently.

C. Preliminary Studies/Progress Report

Provide an account of preliminary studies and/or information that establishes the experience and competence of the investigator to pursue the protocol. (suggested length less than ½ page)

Our principal investigators, Drs. Mindy Rabinowitz, Marc Rosen and Gurston Nyquist have extensive experience and specialized training in treating patients with chronic sinusitis and nasal polyposis. At this time, there is no standardized treatment for these patients and they often require multiple rounds of oral steroids which have associated side effects. The goal of this study is to investigate whether or not the novel use of topical intranasal furosemide can help decrease the use of oral steroids for this population. Collectively, we have the the equipment, expertise and knowledge-base to follow through with this study.

D. Research Design and Methods

Describe the research design and procedures to be used (what, when, how) Include the duration of participation and early termination criteria. Provide a flow diagram or timetable. Procedures, situations, or materials that may be hazardous to personnel and the relevant precautions, should be outlined here. (suggested length not more than 2 pages)

Through a blinded randomized controlled clinical trial, the recurrence rates of nasal polyps in patients with chronic rhinosinusitis with polyps who are undergoing sinus surgery will be compared through their response to therapy with topical furosemide versus placebo. Eligible patients will be recruited through the Otolaryngology Department at Thomas Jefferson University Hospital. During pre-operative clinical visits, eligible patients will be selected and provided the option to participate in the study.

Topical sinus medications have been administered via Mucosal Atomization Device (MAD) in the treatment of chronic rhinosinusitis. Kanowitz et al studied the use of budesonide respules administered via MAD in refractory postoperative

rhinosinusitis[9]. A separate study found that medication administered via the MAD resulted in distribution to the maxillary sinus, ethmoid cavity, and frontal recess post endoscopic sinus surgery[10].

When administering furosemide via the MAD, a total daily dose used in a previous nasal spray trial of 300 mcg was utilized[11]. Patients may administer 75 mcg/0.3 ml to each nostril twice daily to result in the total daily dose of 300 mcg. The volume of 0.3 ml to each nostril is the volume recommended by the manufacturer for intranasal administration via the MAD nasal device.

Performing nasal atomization with 150 mcg twice daily would results in a total exposure of 300 mcg of furosemide daily. Following intranasal administration, a drug may enter systemic circulation through direct local absorption in the nasal mucosa or oral absorption of the swallowed medication[12]. When administering intravenous furosemide it has a threshold dose. No diuretic effect is evident at any dose lower than the threshold dose. The threshold dose for intravenous furosemide is 10 mg in a population with normal renal function[13]. Extrapolating this data, a 300 mcg exposure of furosemide should not result in diuresis. A portion of the drug may also be cleared from the sinuses into the throat and swallowed, making it available for gastrointestinal absorption. Furosemide oral solution has a bioavailability of 60%, of that from an intravenous injection of furosemide[14]. Therefore swallowed medication should not result in therapeutic levels of furosemide.

After obtaining consent, selected patients will be randomized into 2 groups using the balance block randomization method to either treatment group or placebo group and be scheduled for surgery. Balance block randomization involves the preparation of 4 sheets of paper, writing on 2 sheets “F” for “furosemide” and on 2 sheets “P” for “placebo”. The paper sheets will be pooled, placed in a container, and randomly drawn 1 at a time without replacement until all sheets were drawn. The paper sheets will then be placed back into the container and the selection process will be repeated until the sample size is reached. The study investigators will be blinded to the selection process and the randomization will be carried out by the clinical research nurse. A total of 100 patients will be enrolled in the study.

Pre-operatively all patients will receive a 5 day course of 40 mg prednisone, at least one week of and intranasal steroid, and saline irrigation. During a preoperative clinical visit, the degree of sinonasal polyposis will be graded through the Lund Kennedy and Meltzer endoscopic scoring system as well as degree of symptoms through SNOT-22 scores. Also, a demonstration and instructional sheet for how to administer the nasal spray will be distributed at this time.

Then, patients will undergo functional endoscopic surgery as scheduled.

Immediately post-operatively, patients will begin a 6 week course of twice a day nasal spray If assigned to the treatment group they will receive 300 micrograms of furosemide daily. If assigned to the placebo group, they will receive saline. The clinical research nurse will distribute an unmarked bottle of nasal spray to the study patients either in a pre-operative clinical visit or in the recovery room on the day of surgery. Creation of the study drug will be done by AdvancedRx of Plymouth Meeting, Pa. The department research nurse will store and distribute the study drug to the subjects. Post-operatively, patients will also receive a 40mg prednisone taper (40mg for 3 day, 30mg for 3 days, 20 mg for 3 days, 10 mg for 3 days), nasal saline and a 5-day course of omnicef and at least a 6 week course of intranasal corticosteroid spray. Patients will be given a diary to record any doses that were missed.

Patients taking aminoglycosides will be excluded from this trial as furosemide may increase the ototoxic potential of aminoglycosides. Study subjects who require aminoglycoside use during the study treatment period will be instructed to discontinue taking the study drug and will be removed from the study.

Post-operative visits will be scheduled at 1 week, 3 week, 2 month, 4 month and 6 month intervals. The post-operative visits may be scheduled within 4 days of the scheduled interval. Post-operatively, the degree of nasal polyposis will again be graded through the Lund Kennedy and Meltzer endoscopic scoring system as well as degree of symptoms through SNOT-22 scores. These scores will be obtained at the 2, 4 and 6 month visit.
The duration of participation for the study will be 6 months. Early termination criteria are serious adverse reactions, inability to recruit or adequately enroll an adequate number of patients, problems arise in the study medicine's stability or manufacturing and new toxicological findings that affect the benefit-to-risk ratio.

E. Statistical Methods

If not a pilot study, provide biostatistical design, power calculations determining the number of participants , and the proposed analysis. (suggested length: ½ page)

Based on prior randomized controlled clinical trials, the study is powered to achieve at least 80% power. Based on the results published by Hashemian et al.[1], Group sample sizes of 40 in ctrl and 40 in treat achieve 95% power to detect a difference of 38% vs. 79% using two-sided Fisher's Exact Test with significance level 5%. Also based on results published by Passali et al.[2], group sample sizes of 47 in ctrl and 47 in treat achieve 80% power to detect a difference of 30% vs. 6% using two-sided Fisher's Exact Test with significance level 5%.

The primary outcomes will be compared through the independent t test for continuous variables and the Fischer exact test for nominal variables. All statistical analyses will be performed at a significance level of 0.05.

F. Gender/Minority/Pediatric Inclusion for Research

All protocols must include documentation of the inclusion of women and minorities in the research protocol. If women and minorities are not to be included, provide rationale for exclusion.

The study will include women and minorities.

G. Human Subjects

1. Provide number, age range, and health status of the subject population. List criteria for inclusion or exclusion.

100 patients, 18 to 65 years old, chronic rhinosinusitis with sinonasasl polyposis

Inclusion Criteria:

Patients with chronic rhinosinusitis and sinonasal polyposis who are candidates for functional endoscopic sinus surgery

Exclusion Criteria:

Hypersensitivity to furosemide or sulfonamides, pregnancy, history of tinnitus, history of sensorineural hearing loss, poorly controlled diabetes, current diuretic therapy, known electrolyte disorder, currently taking aminoglycosides, BUN and creatinine levels out of the normal range, history of renal disease, allergy to sulfonamides.

2. Identify sources of research material in the form of specimens, records or data.

Patient medical record, physical exam findings (endoscopic scores), SNOT-22 questionnaire,

3. Describe plans for recruitment and consent procedures to be followed.

Patients will be recruited through clinical visits at the Department of Otolaryngology at Thomas Jefferson University Hospital. Informed consent will be obtained at those clinical visits. Potential subjects will be informed of the research and provided a copy of the consent at their office visit with the physician. Either the principal investigator, co-investigators, or the department's research nurse will conduct the consent interview. At that time, one of the investigators will present the study to the subject. The subject will be allowed to read the consent and ask questions. The subject may also have the consent form read aloud to them. The investigator conducting the consent interview will ensure that all sections of the consent form are reviewed with the subject. Subjects will be provided with as much time as they need to review the consent form. If they do not want to sign at the time of this visit, they may bring the consent home with them and come back at a later time to sign.

4. Describe risks and assess likelihood and seriousness.

Since the study involves the standard of care for CRSwP undergoing sinus surgery, the study's risk are limited to the study drug, topical furosemide. As an FDA approved medicine, oral/intravenous furosemide has been shown to have

the following risks: dehydration and fluid/electrolyte imbalance (hyponatremia, hypochloremic alkalosis, hypokalemia, hypomagnesemia or hypocalcemia): dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, arrhythmia, or gastrointestinal disturbances such as nausea and vomiting). In addition furosemide has been shown to cause tinnitus and sensorineural hearing loss, dizziness, headache and blurred vision. Other reactions in decreasing order include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis and fever. Some hematologic and dermatologic reactions have also been reported. Patients allergic to sulfonamides may also be allergic to furosemide due to its incorporated sulfa moiety. That said, review of clinical trials of inhaled furosemide in acute and chronic asthma indicates that it does not induce significant side effects and no diuretic effect has been reported.[8] In prior studies with topical nasal spray use, topical furosemide has be shown have a limited side effect profile including nasal irritation and constipation. It is unlikely that patients enrolled in the study will have side effects or adverse events based on prior studies and if they do the adverse effects will likely be minor.

5. Describe procedures for protecting against or minimizing potential risks.
Patients will be screened closely using the inclusion/exclusion criteria involving health status and prior sensitivity reactions to furosemide or sulfonamides. Also, the patients will be followed closely for adverse reactions during the post-operative period with visits at 1 week, 3 week, 2 month, 4 month and 6 month intervals. Any adverse effect will be documented and if serious appropriate intervention or discontinuation of study drug will be addressed.

6. Describe potential benefits and importance to the subjects and others.
Topical furosemide nasal spray may limit the recurrence of nasal polyposis. If proven effective, it would provide support for a novel use of a well known and affordable drug to create a safe and effective medical therapy to limit the morbidity of recurrence of polyps and multiple surgical procedures as well as an alternative to harmful effects of current therapies involving chronic systemic and topic steroid use.

7. Discuss why risks are reasonable in relation to benefits.
Given the minimal risks of topical furosemide, close follow up with monitoring and limited length of a 2-month treatment course in a 6 month study with the potential benefit of preventing the recurrence of nasal polyposis in this complicated subset of patients, the risks of the study are reasonable in relation to the benefits. If proven effective, this study may change the post-operative management of nasal polyposis and provide patients a safe and effective medical therapy to prevent and limit the morbidity of the recurrence of nasal polyps in chronic rhinosinusitis patients.

H. Data and Safety Monitoring Plan

All protocols that pose greater than minimal risk must have a Data and Safety Monitoring Plan (see DHSP policy G 616 "Independent Monitoring of Investigator-Initiated Clinical Trials."

1. Describe the Data and Safety Monitoring Plan (DSMP)

   a. reporting mechanisms for adverse events to the IRB, FDA, and NIH.
   Investigators will follow all guidelines for reporting to IRB.

   b. adverse event (AE) grading
   Adverse events will be graded by investigators using the CTCAE v.4.

   c. plan for unanticipated AE reporting
   Unanticipated adverse events will be reported to the IRB per the reporting guidelines.

   d. plan for annual reporting of AEs
   Annual reporting of AEs will be done at the time of continuing review.

   e. interim efficacy analysis where appropriate
   If not, just put n/a, no interim efficacy analysis will be done.

2. If applicable, describe the Data and Safety Monitoring Board (DSMB) that will be responsible for monitoring the study. Indicate Chair, members, areas of expertise, frequency of meetings, distribution of reports.
There is no DSMB for this study.

I. Literature Cited

List only literature cited within the text. (suggested length: no more than 12 references)

Date 5/10/2018

Version 6.0

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[2] Passàli D, Bernstein JM, Passàli FM, Damiani V, Passàli GC, Bellussi L. Treatment of Recurrent Chronic Hyperplastic Sinusitis With Nasal Polyposis. *Arch Otolaryngol Head Neck Surg.* 2003;129(6):656-659. doi:10.1001/archotol.129.6.656

[3] Passàli D, Mezzedimi C, Passàli G, C, Bellussi L, Efficacy of Inhalation Form of Furosemide to Prevent Postsurgical Relapses of Rhinosinusal Polyposis. ORL 2000;62:307-310

[4] Michael A. DeMarcantonio, Joseph K. Han, Nasal Polyps: Pathogenesis and Treatment Implications, Otolaryngologic Clinics of North America, Volume 44, Issue 3, June 2011, Pages 685-695, ISSN 0030-6665, http://doi.org/10.1016/j.otc.2011.03.005.

[5] Flint PW, Bruce HH, Lund VJ, et al. *Cummings Otolaryngology–Head & Neck Surgery*. 6th ed. Philadelphia, PA: Mosby; 2015.

[6] P.S. Batra, L. Tong, M.J. Citardi Analysis of comorbidities and objective parameters in refractory chronic rhinosinusitis Laryngoscope, 123 (Suppl 7) (2013), pp. S1–S11

[7] Wynn, R. and Har-El, G. (2004), Recurrence Rates after Endoscopic Sinus Surgery for Massive Sinus Polyposis. The Laryngoscope, 114: 811–813. doi:10.1097/00005537-200405000-00004

[8] Niven AS, Argyros G (2003) Alternate treatments in asthma. Chest 123(4):1254–1265

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11. Hashemian, F., Ghorbanian, M. A., Hashemian, F., Mortazavi, S. A., Sheikhi, M., Jahanshahi, J., & Poorolajal, J. (2016). Effect of topical furosemide on rhinosinusal polyposis relapse after endoscopic sinus surgery: a randomized clinical trial. JAMA Otolaryngology–Head & Neck Surgery, 142(11), 1045-1049.

12. Derendorf, H., & Meltzer, E. O. (2008). Molecular and clinical pharmacology of intranasal corticosteroids: clinical and therapeutic implications. Allergy, 63(10), 1292-1300.

13. Oh, S. W., & Han, S. Y. (2015). Loop diuretics in clinical practice. Electrolytes & Blood Pressure, 13(1), 17-21.

14. Lasix(R) [package insert]. Bridgewater, NJ: Sanofi-Aventis U.S. LLC; 2011.