The prevalence of local IgE elevation and its effect on intranasal capsaicin therapy in the non-allergic rhinitis population

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Protocol Title:	The prevalence of local IgE elevation and its effect on intranasal capsaicin therapy in the non-allergic rhinitis population
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Population:	Non-smoking Adults > 18 years of age with chronic rhinitis
Number of Sites:	Single site
Study Duration:	1 year
Subject Duration:	15 weeks

General Information

Our study aims to determine the therapeutic response of patients with non-allergic rhinitis with local IgE elevation to intranasal capsaicin, the prevalence of non-allergic rhinitis with local IgE elevation in the non-allergic rhinitis population, and to determine the change in intranasal IgE after capsaicin treatment.

Background Information

Rhinitis is inflammation of the nasal lining characterized by 2 or more of the following nasal symptoms: congestion, rhinorrhea, sneezing or itching. Chronic rhinitis is categorized as allergic or non-allergic rhinitis. Allergic rhinitis is driven by an IgE-mediated response to allergens in the environment. Non-allergic rhinitis represents a heterogenous group of disorders whose underlying pathology is not IgE-mediated. Allergy testing distinguishes between allergic and non-allergic rhinitis. Subtypes of non-allergic rhinitis include drug-induced, hormonal, atrophic, gustatory, non-allergic rhinitis with eosinophilia syndrome (NARES), and non-allergic rhinitis with local IgE elevation. This heterogenous group can be divided into conditions that demonstrate nasal inflammation histologically (NARES and non-allergic rhinitis with local IgE elevation) and those that do not. Those that do not are often referred to as non-allergic rhinopathy rather than rhinitis due to the lack of inflammation. Allergic rhinitis is typically best treated with a combination of nasal steroids, nasal antihistamines, oral steroids, and oral antihistamines. Non-allergic rhinitis demonstrating inflammation (NARES and non-allergic rhinitis with local IgE elevation) may best be treated similarly. However, non-allergic rhinopathy tends to be driven by an imbalance in autonomic input. Therefore, ipratropium sprays are currently the mainstay of medical therapy for non-allergic rhinopathy. When medical therapy is insufficient, interventions focusing on the ablation of the parasympathetic innervations of the nasal mucosa are options including vidian neurectomy or cryotherapy of the nerve.

A thorough history and physical can sometimes identify a specific subtype of non-allergic rhinitis to guide therapy. However, certain conditions, such as non-allergic rhinitis with local IgE elevation, cannot be confirmed without further evaluation. Two techniques have recently been proposed to differentiate inflammatory and non-inflammatory subtypes of non-allergic rhinitis: detection of local IgE levels from

mucosal brush biopsy of inferior turbinate and optical rhinometry after intranasal capsaicin challenge. These techniques potentially can be combined to subtype non-allergic rhinitis patients and monitor response to treatment.

Mucosal brush biopsy of the inferior turbinate has been demonstrated to be capable of detecting antigen-specific IgE within the nasal mucosa. [1] In fact, Reisacher et al. in 2014 reported that in a group of 20 patients with chronic, idiopathic, nonallergic rhinitis all were found to have antigen-specific IgE to at least 1 antigen. [2] Other studies have demonstrated that patients with elevated local IgE levels may respond similarly to oral antihistamines and topical nasal steroids as patients with allergic rhinitis. It is this rationale that has led some to propose using nasal provocation testing and local IgE levels in the diagnostic evaluation of patients with non-allergic rhinitis. [3]

Optical rhinometry is a technique which measures the blood flow in nasal vessels reported as optical density (OD). When used with intranasal provocation testing, it is useful in measuring changes in blood flow which correlates with onset of symptoms and increase in nasal mucosal swelling. [4] Additionally, the use of optical rhinometry with intranasal capsaicin challenge has been reported as a viable option in the diagnosis of non-allergic irritant rhinitis. [5]

More recently, intranasal capsaicin has been described as a novel therapeutic option for non-allergic rhinitis [6], and the cellular mechanism underlying its use has been further defined. It has been shown that patients with idiopathic rhinitis have higher baseline levels of transient receptor potential villanoid 1 (TRPV1) within the nasal mucosa [7] and lower thresholds for response to TRPV1 agonists. [8] Treatment with repeated intranasal capsaicin is thought to cause down regulation or degeneration of nerve terminals expressing TRPV1 resulting in a reduction in TRPV1 levels as well as an increase in response threshold to TRPV1 agonists. [8] This translates into a reduction in nasal symptomology that is sustained through 12 weeks post-treatment. [7]

Our current understanding of outcomes after treatment with intranasal capsaicin is incomplete. Most studies analyzing the effect of intranasal capsaicin have evaluated a heterogenous group of non-allergic rhinitis patients with idiopathic rhinitis without distinguishing among subtypes. Consequently, we do not know whether certain subtypes of idiopathic rhinitis are more likely to respond to treatment with intranasal capsaicin treatment than other subtypes. Due to the relative paucity of information regarding therapeutic efficacy of intranasal capsaicin for non-allergic rhinitis, the most recent Cochrane review describes capsaicin as an option for patients with idiopathic, non-allergic rhinitis. [9] We hope to further delineate the group of idiopathic non-allergic rhinitis patients that will benefit from intranasal capsaicin in an effort to refine the treatment algorithm for non-allergic rhinitis.

Objectives

- Primary: To determine the therapeutic response of non-allergic rhinitis patients that have been subtyped as non-allergic rhinitis with local IgE elevation or non-allergic rhinopathy to intranasal capsaicin based on visual analog scale and optical rhinometry
    - The total as well as individual symptom VAS scores at enrollment, 4 weeks post-treatment, and 12 weeks post-treatment will be compared
    - The maximum optical density determined via optical rhinometry at enrollment and 12 weeks post-treatment will be compared
- Secondary: To determine the prevalence of non-allergic rhinitis with local IgE elevation in this study's cohort of patients with non-allergic rhinitis identified by rhinitis history and negative skin

testing for allergic rhinitis, and to determine the change, if any, in intranasal IgE levels after capsaicin treatment.

- The local IgE level obtained from the brush biopsy of the inferior turbinates at enrollment and at 12 weeks post-treatment will be compared

Study Design

- Prospective cohort study
- The study is expected to last 1 year with subject participation lasting 15 weeks.
- Therapeutic response to intranasal capsaicin will be measured using major nasal symptoms on a visual analog scale, as well as optical rhinometry.
  - Nasal symptoms of rhinorrhea, nasal obstruction, nasal itching, and sneezing, will be measured using a visual analog score. Results range from 0-10. The major nasal symptom will be defined as the nasal symptom with the highest score on VAS at screening. The pre- and post-treatment data can be compared to measure change in symptoms.
  - Optical rhinometry: Maximum optical density will be recorded following the initial capsaicin challenge, as well as at 12 weeks post-treatment
- Assessment of efficacy will be based on repeat symptoms scores (nasal symptom inventory pre-treatment and at 4 and 12 weeks, optical rhinometry pre-treatment and 12 weeks post-treatment). Additionally, brush biopsy of the inferior turbinates will be performed pre-treatment and 12 weeks post-treatment in order to determine any change in local IgE levels.
- This study is using previously described methods with good safety profiles. Patients may experience minimal pain and some discomfort with the skin prick test for allergy testing, the mucosal swab for IgE levels, and the intranasal capsaicin.
- Patients will receive skin allergy testing with results and clinic visits with physician at no charge. In addition, study drugs will be provided at no cost to the patient. Although no monetary compensation will be provided for participating in the study, study participants will be reimbursed the fee for parking at all three visits.

Study Population

All patients that present with chronic rhinitis not otherwise classified as allergic based on prior positive skin or blood test to the Texas Sinus Institute will be screened for study inclusion.

Inclusion Criteria:

1. Adult > 18 years of age
2. Chronic rhinitis

Exclusion Criteria:

1. Active smoker
2. Anatomic source of nasal symptoms
3. Chronic rhinosinusitis or other nasal infection
4. History of sinonasal malignancy
5. Pregnancy or lactation
6. Use of medication affecting nasal function (topical steroids, topical anticholinergics, oral antihistamines) in the previous 4 weeks
7. Use or abuse of nasal decongestants.
8. Positive skin prick test for allergic rhinitis

Study Procedures

At the first visit after enrollment:

- Rate major nasal symptoms (rhinorrhea, nasal obstruction, nasal itching, and sneezing) on a visual analog scale
- Complete skin prick allergy testing
- A nasal brushing to determine local IgE levels
- Optical rhinometry with intranasal capsaicin challenge to confirm diagnosis of non-allergic irritant rhinitis[1]

This will be followed by treatment:

- Intranasal capsaicin, 5 applications each delivering 2 micrograms in each nostril, separated by 1 hour.
    - The first treatment will be administered in the clinic to demonstrate how the spray is done, and to monitor for any side effects.
    - The patient will then be provided with 4 additional prefilled syringes with capsaicin to be administered at home.
    - The patient will also be provided with a document that will tell them at what time to administer the medication, and so that they can keep track of how many sprays have been completed.

At week 4 post-treatment (+/- 1 week)

- Rate major nasal symptoms on a visual analog scale
- To reduce visits during the study, the VAS at 4 weeks post-treatment can be done remotely. It will be conducted via phone call, email, or mail according to patient preference.

At week 12 post-treatment (+/- 2 weeks)

- Rate major nasal symptoms on a visual analog scale
- A nasal brushing will be obtained to determine local IgE levels
- Optical rhinometry with intranasal capsaicin challenge[1]

Information gathered for the study will include: personal health information, major nasal symptoms, allergy skin test results, mucosal IgE levels, and optical rhinometry.

- Any physical information (Consent, VAS, etc.) will be stored in a locked filing cabinet within the locked otolaryngology clinic located at 6400 Fannin, Suite 2700. The data gathered will be entered into a password protected excel spreadsheet and saved on a UT issued password protected laptop.

Allergy skin prick testing

- All consented subjects with history consistent with chronic rhinitis will be screened with a skin prick test (Multi-Test II Lincoln Diagnostics, Decatur, IL USA) to common allergens including dust mite, cat hair, grass pollen, insect extracts, fungi/mold extracts, and bermuda grass extract to exclude allergic rhinitis. Those with confirmed negative skin prick testing (ruling out allergic rhinitis) will be eligible for the study.
    - Having a positive reaction to at least one antigen and the positive control will be considered positive testing, and that subject will be excluded from the study

- Having no reaction to all tested antigens except the positive control will be considered negative testing and that subject will be eligible for the study.

Mucosal brush biopsies

- The mucosal local IgE levels will be obtained according to the protocol demonstrated by Reisacher et al.[2]
  - A cytology brush will be used to brush the inferior turbinates (3 spins of the brush against the medial aspect of the inferior turbinates). The brush is then washed in saline and stored at -20C.
  - Antigen specific IgE will be determined using reference lab from the processed sample.

Intranasal capsaicin treatment

- The intranasal capsaicin treatment will be completed according to the protocol for treatment of non-allergic irritant rhinitis with intranasal capsaicin established by Van Gerven et al.[3]
  - Patients will be treated with 5 intranasal doses of capsaicin separated by 1 hour
  - Capsaicin solution (Sigma Chemical, St. Louis, MO USA) will be diluted in 1% ethanol and 0.9% normal saline. A mucosal atomizer device (MAdomizer, Wolfe Tory Medical, Inc, Salt Lake City, UT USA) delivering 100 µL solution will be used to deliver a total dose of 2 µg of capsaicin to each nasal cavity for each application. Each application of capsaicin will be preceded by application of 100 µL of aerosolized 1% lidocaine for anesthesia 15 minutes prior to each planned intranasal capsaicin application.

Data and Safety Monitoring

- Serious adverse events are not anticipated. Patients may experience minimal pain and some discomfort with the skin prick for allergy testing, the mucosal brushing for IgE levels, and the intranasal capsaicin.
- The principal investigator will be notified of any adverse events, protocol deviations, and other problems. These will be addressed immediately by the PI or co-investigators.
- On the first of each month, the PI will review the study to ensure that any events or deviations were reported, to ensure that the study is proceeding strictly according to protocol. The status of the study will be reviewed during a monthly meeting with the rhinologic team which consists of Drs. Luong, Martin Citardi and William Yao.

Statistics

In considering our sample size calculation, we considered our primary outcome as the change in VAS for the major nasal symptom. Using the study by Gerven et al. to guide a sample size calculation, we assumed a success rate of capsaicin to be 75% with success defined as a decrease of at least 30% on the VAS for the major nasal symptom. In their study, they enrolled 33 patients with non-allergic rhinitis and showed a significant response to intranasal capsaicin treatment via VAS. Consequently, we will plan for 33 patients with non-allergic rhinitis to complete this study.

Differences between all continuous descriptive factors and both pretreatment and posttreatment outcome measure scores, between participants with and without local IgE elevation, will be evaluated using Mann Whitney U or chi-square ($\chi 2$) testing where appropriate. Significant improvements in outcome measure scores over time and between pretreatment and posttreatment scores will be evaluated using Wilcoxon signed rank tests. Significant differences will be identified at a conventional 0.050 alpha level.

Ethics

- IRB approval will be sought from CPHS
- Prior to obtaining consent, the study and the subject's participation requirements will be fully explained to the subject. They will be given ample time to read the consent, as well as to ask questions. If needed, a copy of the consent can be provided to take home if additional time is needed to review. Consent will then be obtained after the subject has had adequate time to assess the study.

Data handling and record keeping

- Access to source documents will be limited to study personnel with appropriate training.
- Source documents will be de-identified appropriately. Subjects will be assigned a subject number which will be associated with all data gathered from that subject.
- Subjects will be identifiable through their subject number via an excel spreadsheet which links PHI with subject number. The ability to identify subjects via their subject number will only be available to study personnel with appropriate training.
- All data stored in a password protected excel document will be saved on a UT issued password protected laptop.
- All source documents will be stored in a secured filing cabinet within the locked otolaryngology clinic located at 6400 Fannin, Suite 2700.

Quality control and assurance

- Printed protocol will be available during data collection to ensure that all steps are followed consistently
- Personnel will be available to answer questions regarding questionnaire completion to ensure that all questions are answered and answered appropriately
- Source documents will be saved to confirm integrity of the data transferred to excel documents for analysis.

Publication Plan

- Recruitment for the study is anticipated to begin in April 2019 or once IRB approval is obtained. Recruitment and data collection is expected to last 15 months. Data analysis is projected to take two months. The study is anticipated to be complete and ready for submission to a national meeting for presentation and for publication at the end of 2020.
- Results will not be returned to research subjects

ATTACHMENTS

1. Schematic of Study Design
2. Study Schedule
3. Consent Document
4. Major Nasal Symptom VAS

REFERENCES

1. Lambert EM, Patel CB, Fakhri S, Citardi MJ, Luong A. Optical rhinometry in nonallergic irritant rhinitis: a capsaicin challenge study. *Int Forum Allergy Rhinol*. 2013 Oct;3(10):795-800.

2. Reisacher WR, Bremberg MG. Prevalence of antigen-specific immunoglobulin E on mucosal brush biopsy of the inferior turbinates in patients with nonallergic rhinitis. Int Forum Allergy Rhinol. 2014 Apr;4(4):292-7.
3. Van Gerven L, Alpizar YA, Wouters MM, Hox V, Hauben E, Jorissen M, Boeckxstaens G, Talavera K, Hellings PW. Capsaicin treatment reduces nasal hyperreactivity and transient receptor potential cation channel subfamily V, receptor 1 (TRPV1) overexpression in patients with idiopathic rhinitis. J Allergy Clin Immunol. 2014 May;133(5):1332-9, 1339.e1-3.